

Study Procedures and Assessments

Study assessments and procedures were similar among the phase 2 and phase 3 studies. The phase 3 studies had a 2 to 4 week screening/baseline period. Study visits were QW during the core treatment period in all studies except BA16738 (in patients not on dialysis). In BA16738, patients visited the study clinic Q2W during the anemia correction and evaluation periods and Q4W during the extension period. Samples for determining hemoglobin and hematocrit levels were collected regularly in all studies:

- QW in BA16736 and BA17284
- Q2W (anemia correction period) and Q4W (extension period) in BA16738
- QW (screening through evaluation periods) in BA16739, BA16740, and BA17283
- Q2W (long term safety observation period) in BA16739, BA16740, and BA17283

Concomitant medication information was updated as needed, and adverse event information was collected during the treatment period in all phase 3 studies. Electrocardiograms were performed, and samples for anti-erythropoietin antibody tests, safety laboratory tests, and iron parameters were collected at scheduled intervals throughout all of the studies. In addition, blood pressure and heart rate were assessed at every visit during the core treatment period in all phase 3 studies.

Data Analysis

Analysis Populations

General rules for inclusion in or exclusion from an efficacy analysis population were similar among the phase 3 studies. For the phase 3 studies, efficacy was analyzed primarily in the intent-to-treat (ITT), eligible, and per-protocol (PP) populations. The ITT population was defined for all studies as all patients randomized. The eligible and PP populations are described further below:

Eligible Population

In anemia correction studies, the eligible population was defined as the subset of the ITT population after exclusion based on the following study-specific protocol violations at baseline (exclusion criteria):

- BA16736
 - Hemoglobinopathies or hemolysis
 - RBC transfusions or blood loss requiring treatment prior to randomization
- BA16738
 - Hemoglobinopathies, hemolysis, or RBC transfusions within 8 weeks before screening or during the screening period
 - Immunosuppressive therapy within 12 weeks of screening, except cyclosporine, mono/polyclonal antibodies, and chronic corticosteroids

In hemoglobin maintenance studies (BA16739, BA16740, BA17283 and BA17284), the definition for eligible population differed from the definition in anemia correction studies in that patients who did not receive at least one dose of the study medication after randomization was also excluded, in addition to exclusion based on the following study-specific protocol violations at baseline (exclusion criteria):

- Lack of a stable baseline hemoglobin (absolute difference < 1.0 g/dL between mean hemoglobin at weeks -4 and -3 and values at weeks -2 and -1); hemoglobinopathies, hemolysis, or blood transfusion at baseline.
- Inadequate iron stores (mean serum ferritin < 100 ug/L and mean TSAT $< 20\%$, or mean hypochromic RBC $> 10\%$) at baseline (weeks -4 and -3)

PP Population

In both the anemia correction and the hemoglobin studies, the PP population was defined as a subset of the eligible population after excluding for the following pre-specified protocol violations:

- BA16736 (Anemia Correction)
 - Patients with RBC transfusions (not related to lack of effect of study medication) or blood loss requiring treatment prior to randomization or within weeks 1-24, before achieving hemoglobin response
 - Patients who fulfilled the following exclusion criteria before the first dose: hemoglobinopathies or hemolysis
 - Patients who had less than 75% of the scheduled post-baseline hemoglobin measurements during the first 24 weeks (through day 173)
 - Patients who received an incorrect dose or missed an administration on two consecutive applications or more than three times before day 173 (24 weeks of treatment)
- BA16738 (Anemia Correction)
 - RBC transfusions (not related to lack of effect of study medication) or blood loss (bleeding episode or surgery) within 8 weeks before randomization or within weeks 1-28
 - Hemoglobinopathies or hemolysis, administration of immunosuppressive therapy other than cyclosporine, mono/polyclonal antibodies, or chronic corticosteroids
 - Having fewer than 75% of the scheduled post-baseline hemoglobin measurements during the first 28 weeks, or fewer than four during evaluation
 - Incorrect or missing dose on two consecutive occasions, or more than three times before week 28; receiving an erythropoietin product not specified in the protocol during 2 consecutive weeks between week 1 and week 28
 - Erythropoietin therapy within 12 weeks prior to screening or dialysis therapy between week 18 and week 28
- BA16739, BA16740, BA17283, BA17284 (Hemoglobin Maintenance)
 - Lack of a stable baseline hemoglobin (absolute difference < 1.0 g/dL between mean hemoglobin at weeks -4 and -3 and values at weeks -2 and -1)
 - Inadequate iron stores at baseline (weeks -4 and -3) or at evaluation (mean serum ferritin < 100 ug/L AND mean TSAT $< 20\%$, or mean hypochromic RBC $> 10\%$)
 - RBC transfusion (not related to lack of effect of study medication) during baseline or within weeks 21 to 33.

- Patients receiving RBC transfusions or undergoing major surgery (including transplantation) after week 33 were included in the PP population.
- In these patients, hemoglobin values after the event were censored and: the last observed value was carried forward in BA17283 and BA16740, or regarded as missing in BA16739 and BA17284.
- Hemoglobinopathies or hemolysis at baseline; fewer than five recorded hemoglobin values during evaluation; missing a dose during weeks 26 to 35.

Efficacy Analyses in Phase 3 Correction Studies

Primary Efficacy

Summaries and plots of hemoglobin over time or hemoglobin change from baseline over time were produced using monthly time points. The analyses were limited to the end of the anemia correction period (BA16736) and end of the evaluation period (BA16738) so that only complete data was used.

- The primary efficacy parameter in the phase 3 anemia correction studies (BA16736 and BA16738) was the hemoglobin response rate. Response was defined as an increase in hemoglobin of at least 1.0 g/dL compared to baseline and a hemoglobin of at least 11.0 g/dL without RBC transfusion during the anemia correction period (first 24 weeks after first dose) of BA16736, and during the anemia correction and evaluation periods (first 28 weeks after first dose) of BA16738.
- The average baseline value was estimated using all values recorded between the day of first study dose and the previous 20 days (protocol requirement was 2 values taken at least 1 day apart). The value on the day of first dose was included in the baseline calculation as this assessment was performed before the first dose was given.
- The observed response rate during the anemia correction or anemia correction and evaluation study period was shown and presented graphically. The confidence intervals for the response rate were calculated using the Clopper-Pearson method.
- BA16738 had a second primary efficacy parameter: the difference in the mean change in hemoglobin between the baseline and evaluation periods. The evaluation period was week 20 up to and including week 28 (after the 18-week anemia correction period). The average hemoglobin for each individual during this evaluation period was estimated by AUC.

Secondary Efficacy

Secondary efficacy analyses in the anemia correction studies included hemoglobin values and their change from baseline over time and incidence of RBC transfusion. The anemia correction studies also assessed time to hemoglobin response (via Kaplan-Meier methods). Censoring occurred on the day of RBC transfusion or at the time of last hemoglobin determination for patients who withdrew early from the study or who reached the end of the anemia correction period without achieving the criteria for response.

Efficacy Analyses in Phase 3 Maintenance Studies

Primary Efficacy

Summaries and plots of hemoglobin over time and hemoglobin change from baseline over time were produced using monthly time points. In addition, outputs of the number and percentage of patients with mean hemoglobin during the evaluation period within, below, or above target range were created.

- The primary efficacy variable in the hemoglobin maintenance studies was the change in hemoglobin between baseline and the evaluation period.
- The baseline period was defined as all assessments between the day of first study dose and the previous 30 days. The hemoglobin value on the day of first dose was included in the baseline calculation, as this assessment was performed before the first dose is given. The evaluation period was between 29 and 36 weeks of treatment (after a 28-week titration period).
- The average hemoglobin for each individual during the baseline and the evaluation periods was calculated using the AUC method. Subtracting the individual baseline value from the evaluation period value gave the final endpoint.

Secondary Efficacy

Standard summary tables using means, standard deviations, percentiles, minima and maxima were produced by visit for:

- Number of patients maintaining their average hemoglobin during the evaluation period within ± 1 g/dL of their average baseline concentration,
- Incidence of RBC transfusions during the dose titration and evaluation periods.

Missing Data

Efficacy data missing at the end of the evaluation period (i.e., the last measured hemoglobin value was before week 36, or possibly before start of the evaluation period for the ITT and eligible population analyses) were handled using the last observation carried forward (LOCF) method. It was assumed that missing hemoglobin assessments would generally follow one or several hemoglobin values outside the target range, since patients may have been withdrawn if hemoglobins were not maintained. Carrying forward hemoglobin values outside the target range can therefore be seen as a conservative approach. Values missing between recorded assessments were automatically interpolated by the trapezoidal rule. If a blood transfusion occurred during the titration or evaluation period, the hemoglobin values measured in the following 3 weeks were replaced by the hemoglobin value measured immediately before the transfusion to correct for the increase caused by the transfusion.

Test of Non-Inferiority

Comparisons were made between Mircera Q2W vs reference medication and, when applicable, Mircera Q4W vs reference medication.

The test of the primary endpoint (hemoglobin change from baseline) was based on an ANCOVA model used to compare each Mircera group to the reference group. The independent variable in the model was treatment group; hemoglobin at baseline was a covariate in all studies. Additional covariates (e.g., geographical region and route of administration) were added as appropriate.

Two-sided confidence intervals for the difference between treatments in mean change in hemoglobin between the baseline and evaluation periods were calculated using the estimates from this model. A 95% confidence level was used for BA16738, BA17283 and BA17284. The confidence level of 97.5% was used for BA16739 and BA16740, in order to adjust for multiplicity resulting from the independent comparisons of two Mircera groups with one reference group.

In each case, the Mircera treatment was regarded as non-inferior to the reference group if the lower limit of the CI was greater than -0.75 g/dL. A p-value for the non-inferiority test was derived via the t-test.

Subgroup Analyses

The summaries of hemoglobin change from baseline, average hemoglobin over time, and responders were also produced for the following subgroups of patients in the phase 3 studies:

- Dialysis type (hemodialysis, peritoneal dialysis, not on dialysis),
- Medication administration type (IV, SC),
- Previous erythropoietin (epoetin alfa, epoetin beta, darbepoetin alfa),
- Age (<65, 65 - 74, = 75),
- Weight (<65, 65 - 79, = 80),
- Gender (male, female),
- Race (Black, Caucasian, Oriental, other),
- Ethnicity (Hispanic, non-Hispanic),
- Geographic region (US, non-US),
- Etiology of CRF (diabetes, glomerulonephritis, hypertension),
- Diabetes status (diabetic, non-diabetic),
- Iron status (iron deficient, iron replete).

6.1.4 Efficacy Findings

Phase 3 Correction Studies

The two active-controlled, randomized, anemia correction studies (IV, vs epoetin in BA16736; SC, vs darbepoetin alfa in BA16738) were conducted open-label at multiple sites worldwide in patients not previously treated with an erythropoietin product.

Subject Exclusion for Elevated CRP

Subject selection criteria in all studies (phase 2 and phase 3) specified exclusion for an elevated C-reactive protein (CRP) level. In 5 of the 6 phase 3 studies (BA16736, BA16739, BA16740, BA17283, and BA17284), patients were excluded for CRP > 30 mg/L; in the remaining phase 3 study (BA16738), patients were excluded for CRP > 15 mg/L.

Exclusion for elevated CRP was based on active laboratory screening, which was repeated every 8 weeks in all phase 3 studies as part of scheduled subject monitoring. Patients were excluded at rates < 5%. **Table 4** shows the proportions of patients excluded based on elevated CRP, and **Table 5** compares the patient distribution across different CRP levels.

Table 4: CRP Exclusion in Phase 3 Studies

Study	Description	Screened	Excluded
BA16736	anemia correction in dialysis, exclude for CRP > 30 mg/L	234	4 (1.7%)
BA16738	anemia correction in non-dialysis, exclude for CRP > 15 mg/L	498	21 (4.2%)
BA16739	hemoglobin maintenance in dialysis, conversion from epoetin, exclude for CRP > 30 mg/L	1115	45 (4.0%)
BA16740	hemoglobin maintenance in dialysis, conversion from epoetin, exclude for CRP > 30 mg/L	817	18 (2.2%)
BA17283	hemoglobin maintenance in dialysis, conversion from darbepoetin, exclude for CRP > 30 mg/L	444	11 (2.5%)
BA17284	hemoglobin maintenance in dialysis, conversion from epoetin, exclude for CRP > 30 mg/L	519	19 (3.7%)
All Phase 3 Studies		3627	118 (3.3%)

Table 5: CRP Distribution at Phase 3 Screening

EPO	Baseline Levels of C-Reactive Protein			
	NA	< 10 mg/L	10 & < 30 mg/L	> 30 mg/L
Mircera	43 (2.4%)	1319 (74%)	398 (22%)	29 (1.6%)
Reference	24 (2.5%)	720 (76%)	190 (20%)	14 (1.5%)

EPO = erythropoietin product; CRP = C-reactive protein; NA = value not available

Review Comments:

Active inflammation (including infection), with or without a documented elevation in the CRP level, is an important subject exclusion criterion since active inflammation may increase the risk of serious treatment-related adverse events.

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- The number of patients excluded from participation in a phase 3 study was not a significant fraction of those screened (3.3%). It appears unnecessary to specify in the product label for Mircera that a CRP level should be obtained to determine treatment eligibility.

Study Populations Overview

A total of 505 patients were randomized into the phase 3 anemia correction studies. The number of patients entering and completing the anemia correction period of BA16736 and BA16738 is presented in **Table 6**. A breakdown of the study population by route of administration, mode of

dialysis, administration regimen, and geographical region is provided in Table 7. A summary of patient withdrawals is presented in Table 8.

Table 6: Patient Disposition (Phase 3 Anemia Correction)

Correction Studies	Randomized	Completed the Correction Period
BA16736		
RO0503821 1x/2 wk IV	135	124
Reference (epoetin alfa or beta)	46	41*
BA16738		
RO0503821 1x/2 wk SC	162	145
Reference (darbepoetin alfa)	162	153

*Includes one patient not randomized; 40 of 46 randomized patients completed the correction period.

Table 7: Overview of Study Population, Phase 3 Correction Studies

	BA16736			BA16738	
	RO0503821 1*/2 weeks (N =135)	Reference (N =46)	Not Randomized (N =1)	RO0503821 1*/2 weeks (N =162)	Reference (N =162)
Route of Study Drug Administration					
IV	135 (100.0%)	46 (100.0%)	1 (100.0%)	161 (99.4%)	162 (100.0%)
SC				1 (0.6%)	
Not Available					
Mode of Current Dialysis					
Hemodialysis	132 (97.8%)	46 (100.0%)	1 (100.0%)		
Peritoneal Dialysis	3 (2.2%)				
Not yet on Dialysis				162 (100.0%)	162 (100.0%)
Schedule of Study Drug Administration					
<=1*/week		46 (100.0%)	1 (100.0%)		162 (100.0%)
1*/2 weeks	135 (100.0%)			162 (100.0%)	
Geographical Region					
USA	4 (3.0%)	2 (4.3%)		57 (35.2%)	58 (35.8%)
non-USA	131 (97.0%)	44 (95.7%)	1 (100.0%)	105 (64.8%)	104 (64.2%)

Table 8: Summary of Withdrawals in the Correction Studies (ITT Population)

	BA16736		BA16738	
	RO0503821 1*/2 weeks (N =135)	Reference (N =46)	RO0503821 1*/2 weeks (N =162)	Reference (N =162)
Safety	2 (1.5%)	0	7 (4.3%)	5 (3.1%)
Abnormality of Laboratory Test	0	0	0	0
Adverse Event (a)	0	0	3 (1.9%)	5 (3.1%)
Death	2 (1.5%)	0	4 (2.5%)	0
Non-Safety	9 (6.7%)	6 (13.0%)	10 (6.2%)	4 (2.5%)
Insufficient Therapeutic Response	0	0	1 (0.6%)	1 (0.6%)
Early Improvement	0	0	0	0
Violation of Selection Criteria at Entry	0	0	0	0
Other Protocol Violation	0	0	0	0
Refused Treatment (b)	2 (1.5%)	1 (2.2%)	3 (1.9%)	1 (0.6%)
Failure to Return	0	0	4 (2.5%)	0
Other	7 (5.2%)	5 (10.9%)	2 (1.2%)	2 (1.2%)
Total	11 (8.1%)	6 (13.0%)	17 (10.5%)	9 (5.6%)

(a) includes intercurrent illness; (b) includes "did not cooperate" and "withdrew consent"

Analysis Populations

Phase 3 efficacy analysis populations included the ITT, PP, and eligible populations (Table 9). Discussions of primary efficacy analyses in anemia correction focus on the ITT population.

Table 9: Summary of Analysis Populations, Phase 3 Correction Studies

Analysis Population	BA16736		Not Randomized	BA16738	
	RO0503821 1*/2 weeks	Reference		RO0503821 1*/2 weeks	Reference
All Patients	135 (100.0%)	46 (100.0%)	1 (100.0%)	162 (100.0%)	162 (100.0%)
Intent to Treat	135 (100.0%)	46 (100.0%)	0 (0.0%)	162 (100.0%)	162 (100.0%)
Safety	135 (100.0%)	46 (97.9%)	0 (0.0%)	161 (99.4%)	162 (100.0%)
Eligible	134 (99.3%)	45 (95.7%)	0 (0.0%)	160 (98.8%)	161 (99.4%)
Per Protocol	119 (88.1%)	36 (76.6%)	0 (0.0%)	139 (85.8%)	144 (88.9%)

Baseline Demographic Characteristics

Treatment groups within each study were generally well balanced with respect to demographic characteristics. Baseline demographic characteristics are presented in **Table 10** (ITT population).

Table 10: Demographic Data (Phase 3 Correction, ITT Population)

	BA16736		BA16738	
	RO0503821 1*/2 weeks (N =135)	Reference (N =46)	RO0503821 1*/2 weeks (N =162)	Reference (N =162)
Gender				
Female	53 (39.3%)	14 (30.4%)	92 (56.8%)	82 (50.6%)
Male	82 (60.7%)	32 (69.6%)	70 (43.2%)	80 (49.4%)
Race				
Black	17 (12.6%)	7 (15.2%)	35 (21.6%)	19 (11.7%)
Caucasian	106 (78.5%)	33 (71.7%)	113 (69.8%)	131 (80.9%)
Oriental	8 (5.9%)	3 (6.5%)	7 (4.3%)	9 (5.6%)
Other	4 (3.0%)	3 (6.5%)	7 (4.3%)	3 (1.9%)
Ethnicity				
Hispanic	4 (3.0%)		16 (9.9%)	18 (11.1%)
Non-Hispanic	131 (97.0%)	46 (100.0%)	146 (90.1%)	144 (88.9%)
Age [Years]				
N	135	46	162	162
Mean	54.7	53.4	63.9	66.9
Std. Dev.	14.43	15.19	14.11	12.80
Median	54.0	54.5	67.0	69.0
Min-Max	18 - 89	18 - 80	20 - 90	26 - 89
Age Category [Years]				
<65	99 (73.3%)	35 (76.1%)	70 (43.2%)	62 (38.3%)
65-74	23 (17.0%)	6 (13.0%)	44 (27.2%)	48 (29.6%)
>=75	13 (9.6%)	5 (10.9%)	48 (29.6%)	52 (32.1%)
Body Weight [kg]				
N	135	46	162	162
Mean	67.9	73.9	76.8	80.5
Std. Dev.	14.10	15.62	16.22	19.48
Median	66.0	71.9	74.5	75.8
Min-Max	43 -106	42 -105	45 -130	42 -159
Body Weight Category [kg]				
<65	65 (48.1%)	16 (34.8%)	35 (21.6%)	35 (21.6%)
65-<80	41 (30.4%)	13 (28.3%)	65 (40.1%)	57 (35.2%)
>=80	29 (21.5%)	17 (37.0%)	62 (38.3%)	70 (43.2%)

Baseline Disease Characteristics

Baseline parameters used to characterize patient disease status included primary etiology of CRF, use of previous erythropoietin, previous and concomitant iron supplementation, and iron parameters.

Baseline Disease and Treatment

Baseline disease characteristics are presented in **Table 11** (ITT population). The most common primary causes of renal failure were diabetes, glomerulonephritis, and hypertension/large vessel disease, the rates of which were similar among treatment groups in BA16738. In BA16736, the percentage of patients with diabetes was dissimilar between groups: 21% in the Mircera group compared with 28% in the reference group.

**Table 11: Summary of Disease and Treatment Status at Baseline
Phase 3 Correction Studies (ITT Population)**

	BA16736		BA16738	
	RO0503821 1*/2 weeks (N =135)	Reference (N =46)	RO0503821 1*/2 weeks (N =162)	Reference (N =162)
Primary Cause(s) of Renal Failure				
Diabetes	28 (20.7%)	13 (28.3%)	73 (45.1%)	79 (48.8%)
Glomerulonephritis	33 (24.4%)	13 (28.3%)	15 (9.3%)	19 (11.7%)
Secondary Glomerulonephritis / Vasculitis	5 (3.7%)	1 (2.2%)	2 (1.2%)	3 (1.9%)
Interstitial nephritis / Pyelonephritis	12 (8.9%)	5 (10.9%)	9 (5.6%)	10 (6.2%)
Hypertension / Large vessel disease	28 (20.7%)	12 (26.1%)	65 (40.1%)	72 (44.4%)
Polycystic kidney disease/ (adult type, dominant)	16 (11.9%)	1 (2.2%)	7 (4.3%)	9 (5.6%)
Other hereditary / Congenital diseases	4 (3.0%)		2 (1.2%)	2 (1.2%)
Neoplasms / Tumors				1 (0.6%)
Other	5 (3.7%)	1 (2.2%)	14 (8.6%)	11 (6.8%)
Undefined etiology	17 (12.6%)	5 (10.9%)	12 (7.4%)	5 (3.1%)
Study Day of First Dialysis				
N	135	46		
Mean	-775	-760		
Std. Dev.	1412.6	1415.9		
Median	-166	-113		
Min-Max	-8359 - 11	-7716 - -19		
Mode of Current Dialysis				
Hemodialysis	132 (97.8%)	46 (100.0%)		
Peritoneal Dialysis	3 (2.2%)			
Not yet on Dialysis			162 (100.0%)	162 (100.0%)
Vascular Access Type (Hemodialysis, n)				
Arteriovenous fistula	106 (80.3%)	35 (76.1%)		
Arteriovenous graft	9 (6.8%)	4 (8.7%)		
Indwelling (tunneled) catheter	17 (12.9%)	7 (15.2%)		
Peritoneal Dialysis Type (n)				
CAPD	3 (100.0%)			
Route of Study Drug Administration				
IV	135 (100.0%)	46 (100.0%)	161 (99.4%)	162 (100.0%)
SC			1 (0.6%)	
Not Available				

Iron Supplementation

In BA16736, patients were to be administered iron during the entire study period including screening, according to the study protocol. Therefore, previous or previous/concomitant iron supplementation at baseline was between 96% and 100% in each treatment group. In BA16738, patients were administered iron supplementation as necessary; previous/concomitant iron supplementation at baseline was 55% in the Mircera group and 54% in the reference group. The use of these supplements was well balanced between treatment groups within each study, as presented in **Table 12**.

Table 12: Iron Supplementation at Baseline (Phase 3 Correction, ITT Population)

	BA16736		BA16738	
	R00503821		R00503821	
	1 ¹ / ₂ weeks (N =135) No. (%)	Reference (N =46) No. (%)	1 ¹ / ₂ weeks (N =162) No. (%)	Reference (N =162) No. (%)
ALL CLASSES				
Total Pts with at Least one Treatment	129 (95.6)	46 (100.0)	89 (54.9)	87 (53.7)
Total Number of Treatments	158	55	99	102
ANTI-ANEMIC AGENTS				
Total Pts with at Least one Treatment	129 (95.6)	46 (100.0)	89 (54.9)	87 (53.7)
IRON SUCROSE	98 (72.6)	37 (80.4)	23 (14.2)	22 (13.6)
FERROUS SULFATE	22 (16.3)	6 (13.0)	33 (20.4)	37 (22.8)
FERROUS GLUCONATE	12 (8.9)	4 (8.7)	20 (12.3)	15 (9.3)
FERRIC HYDROXIDE	12 (8.9)	2 (4.3)		1 (0.6)
IRON DEXTRAN	2 (1.5)	2 (4.3)	2 (1.2)	4 (2.5)
IRON POLYMALTOSE	5 (3.7)	1 (2.2)	2 (1.2)	2 (1.2)
FERROUS FUMARATE	1 (0.7)	1 (2.2)	5 (3.1)	2 (1.2)
ASCORBIC ACID/ FERROUS SULFATE			3 (1.9)	3 (1.9)
POLYSACCHARIDE-IRON COMPLEX			3 (1.9)	3 (1.9)
IRON SUCCINYL-PROTEIN COMPLEX				4 (2.5)
CALCIUM PHOSPHATE/ FERROUS FUMARATE/ MULTIVITAMIN NOS	3 (2.2)			
FERRIC OXIDE			1 (0.6)	2 (1.2)
*FERROUS GLYCINE SULFATE/POLYSACCHARIDE-IRON COMPLEX				2 (1.2)
ASCORBIC ACID/CYANOCOBALAMIN/ FERROUS SULFATE/FOLIC ACID	1 (0.7)	1 (2.2)		
FERROUS GLYCINE SULFATE			2 (1.2)	
IRON				2 (1.2)
IRON/MANNITOL/OVALBUMIN			1 (0.6)	1 (0.6)
*FERROUS FUMARATE/IRON DEXTRAN/IRON POLYMALTOSE/IRON SUCROSE				1 (0.6)
ASCORBIC ACID/CARBONYL IRON			1 (0.6)	
ASCORBIC ACID/CARBONYL IRON/CYANOCOBALAMIN/FOLIC ACID				1 (0.6)
FERRITIN			1 (0.6)	
FERROUS CHLORIDE		1 (2.2)		
FERROUS SULFATE/ INTRINSIC FACTOR/ *LIVER EXTRACT/MULTIVITAMIN NOS	1 (0.7)			
FERROUS SULFATE/SODIUM ASCORBATE				1 (0.6)
Total Number of Treatments	157	55	98	102
VITAMINS AND MINERALS				
Total Pts with at Least one Treatment	1 (0.7)		1 (0.6)	
IRON/ MULTIVITAMIN NOS			1 (0.6)	
MINERALS/ MULTIVITAMIN NOS	1 (0.7)			
Total Number of Treatments	1		1	

Hemoglobin and Iron Parameters

There were no clinically relevant differences in iron parameters or hemoglobins between treatment groups within any of the studies. The majority of patients enrolled were determined to be iron replete, and hemoglobin values reflected the disease status in the patient population. Baseline laboratory parameters are presented for the ITT population in **Table 13**. Hemoglobin and iron parameter values were similar in the eligible and PP populations.

**Table 13: Baseline Hemoglobin and Iron Parameters
Phase 3 Correction Studies (ITT Population)**

	BA16736		BA16738	
	RO0503821 1*/2 weeks (N =135)	Reference (N =46)	RO0503821 1*/2 weeks (N =162)	Reference (N =162)
Hemoglobin [g/dL]				
N	135	46	162	162
Mean	9.39	9.40	10.22	10.15
Std. Dev.	0.876	0.817	0.596	0.693
Median	9.35	9.28	10.37	10.33
Q1-Q3	8.6 - 10.1	8.7 - 10.2	9.8 - 10.7	9.8 - 10.7
Min-Max	7.7 - 11.3	8.1 - 10.9	8.4 - 11.1	8.0 - 11.3
Serum Iron [umol/L]				
N	135	46	162	162
Mean	13.92	14.37	13.65	13.49
Std. Dev.	4.776	5.274	7.482	5.636
Median	13.25	14.27	12.44	12.97
Q1-Q3	11.1 - 16.2	10.5 - 16.9	9.6 - 16.5	10.3 - 15.2
Min-Max	3.7 - 37.7	5.9 - 30.1	5.7 - 79.2	5.0 - 60.4
Ferritin [ug/L]				
N	135	46	162	162
Mean	479.49	426.22	214.92	240.64
Std. Dev.	382.156	330.741	161.120	197.588
Median	376.33	325.79	174.67	185.83
Q1-Q3	225 - 625	186 - 582	108 - 271	129 - 284
Min-Max	46 - 2807	81 - 1500	12 - 928	18 - 1481
Transferrin Saturation [%]				
N	135	46	161	161
Mean	32.15	30.74	26.25	26.10
Std. Dev.	12.420	12.650	12.452	12.971
Median	29.40	26.73	23.67	23.67
Q1-Q3	24.7 - 37.4	21.3 - 40.3	20.0 - 30.7	20.3 - 29.3
Min-Max	11.3 - 84.8	12.7 - 72.1	11.6 - 145.3	9.9 - 155.5

Baseline Hemoglobin and Iron Stores

Patients were required to have mean baseline hemoglobins between 8 and 11 g/dL for entry into the phase 3 anemia correction studies (BA16736 and BA16738). Mean hemoglobin at baseline was approximately 9.4 g/dL in each of the BA16736 treatment groups and 10.2 g/dL in each of the BA16738 treatment groups. Median hemoglobins were also well balanced between treatment groups within each study: 9.3 g/dL in BA16736 and 10.3 g/dL in BA16738.

Adequate iron status at study entry was defined as serum ferritin over 100 ug/L or TSAT above 20% (or hypochromic red cells < 10%) in all phase 3 studies. Baseline values were adequate and comparable among treatment groups within each of the anemia correction studies:

- Median values for ferritin were: 376 ug/L (Mircera) and 326 ug/L (reference) in BA16736; 175 ug/L (Mircera) and 186 ug/L (reference) in BA16738.

- TSAT median values were: 29% (Mircera) and 27% (reference) in BA16736; 24% in each treatment group of BA16738.

Serum iron levels were comparable among treatment groups in the anemia correction studies: median values were 13.3 $\mu\text{mol/L}$ (Mircera) and 14.3 $\mu\text{mol/L}$ (reference) in BA16736; and 12.4 $\mu\text{mol/L}$ (Mircera) and 13.0 $\mu\text{mol/L}$ (reference) in BA16738. Baseline hemoglobin values and iron parameters are shown in Table 14.

**Table 14: Summary of Baseline Hemoglobin and Iron Parameters
Phase 3 Correction Studies (ITT Population)**

	BA16736		BA16738	
	RO0503821 1*/2 weeks (N =135)	Reference (N =46)	RO0503821 1*/2 weeks (N =162)	Reference (N =162)
Hemoglobin [g/dL]				
N	135	46	162	162
Mean	9.39	9.40	10.22	10.15
Std. Dev.	0.876	0.817	0.596	0.693
Median	9.35	9.28	10.37	10.33
Q1-Q3	8.6 - 10.1	8.7 - 10.2	9.8 - 10.7	9.8 - 10.7
Min-Max	7.7 - 11.3	8.1 - 10.9	8.4 - 11.1	8.0 - 11.3
Serum Iron [$\mu\text{mol/L}$]				
N	135	46	162	162
Mean	13.92	14.37	13.65	13.49
Std. Dev.	4.776	5.274	7.482	5.636
Median	13.25	14.27	12.44	12.97
Q1-Q3	11.1 - 16.2	10.5 - 16.9	9.6 - 16.5	10.3 - 15.2
Min-Max	3.7 - 37.7	5.9 - 30.1	5.7 - 79.2	5.0 - 60.4
Ferritin [$\mu\text{g/L}$]				
N	135	46	162	162
Mean	479.49	426.22	214.92	240.64
Std. Dev.	382.156	330.741	161.120	197.588
Median	376.33	325.79	174.67	185.83
Q1-Q3	225 - 625	186 - 582	108 - 271	129 - 284
Min-Max	46 - 2807	81 - 1500	12 - 928	18 - 1481
Transferrin Saturation [%]				
N	135	46	161	161
Mean	32.15	30.74	26.25	26.10
Std. Dev.	12.420	12.650	12.452	12.971
Median	29.40	26.73	23.67	23.67
Q1-Q3	24.7 - 37.4	21.3 - 40.3	20.0 - 30.7	20.3 - 29.3
Min-Max	11.3 - 84.8	12.7 - 72.1	11.6 - 145.3	9.9 - 155.5

Iron Deficiency During Study

Iron deficiency in BA16736 and BA16738 is shown by month in Table 15 (ITT population). In BA16736, IV iron supplementation was mandatory throughout the study. Mean and median values for ferritin and TSAT were maintained well within adequate levels (defined as ferritin values between 100 and 800 $\mu\text{g/L}$; TSAT between 20 and 50% during the study, in all analysis populations. Despite variation in individual TSAT and ferritin levels, iron deficiency, defined as

patients with TSAT levels below 20% and ferritin levels below 100 ug/L occurred in only 1 (1%) to 6 (5%) patients in the Mircera group and in 1 (2%) to 4 (9%) patients in the reference group.

**Table 15 Summary of Iron Deficiency During Study
Phase 3 Correction Studies (ITT Population)**

	BA16736		BA16738	
	RO0503821 1*/2 weeks (N =135)	Reference (N =46)	RO0503821 1*/2 weeks (N =162)	Reference (N =162)
Patients with TSAT < 20%				
Baseline	14 (10.4%)	8 (17.4%)	40 (24.8%)	38 (23.6%)
Month 1	NA	NA	72 (50.0%)	97 (63.8%)
Month 2	25 (20.0%)	14 (31.8%)	71 (47.0%)	72 (47.7%)
Month 3	23 (18.0%)	8 (18.2%)	75 (51.7%)	62 (41.9%)
Month 4	NA	NA	59 (39.9%)	46 (31.1%)
Month 5	16 (13.0%)	3 (7.1%)	50 (33.8%)	39 (25.0%)
Month 6	10 (8.3%)	7 (17.1%)	40 (27.2%)	29 (19.1%)
Month 7	NA	NA	33 (23.4%)	39 (26.0%)
Patients with FERTN < 100 ng/mL				
Baseline	5 (3.7%)	2 (4.3%)	30 (18.5%)	33 (20.4%)
Month 1	NA	NA	61 (43.0%)	78 (51.0%)
Month 2	6 (4.6%)	6 (13.3%)	72 (47.4%)	67 (44.4%)
Month 3	10 (7.9%)	4 (9.1%)	72 (47.7%)	55 (35.9%)
Month 4	NA	NA	56 (38.1%)	35 (23.2%)
Month 5	5 (4.1%)	2 (4.8%)	44 (29.5%)	26 (16.6%)
Month 6	4 (3.3%)	3 (7.3%)	25 (16.8%)	18 (11.8%)
Month 7	NA	NA	25 (17.5%)	23 (15.2%)
Patients with TSAT < 20% and FERTN < 100 ng/mL				
Baseline			6 (3.7%)	6 (3.7%)
Month 1	NA	NA	34 (24.3%)	53 (35.3%)
Month 2	3 (2.4%)	4 (9.1%)	39 (26.2%)	39 (26.2%)
Month 3	6 (4.8%)	1 (2.3%)	41 (28.5%)	32 (21.9%)
Month 4	NA	NA	24 (16.8%)	16 (10.9%)
Month 5			20 (13.6%)	12 (7.7%)
Month 6	1 (0.9%)	1 (2.4%)	11 (7.5%)	5 (3.4%)
Month 7	NA	NA	7 (5.1%)	9 (6.1%)

Dose Adjustments

Slightly greater numbers of patients in the reference (darbepoetin alfa or epoetin) groups had dose adjustments in the anemia correction period compared to patients in the Mircera groups, as shown in **Table 16**. Dose changes (up or down) occurred more frequently with the reference agents than with Mircera (61% up and 88% down, reference agents; 44% up and 76% down, Mircera).

Dose increases only were more common with Mircera than with the reference agents. In BA16736, a lower percentage of patients in the Mircera group (8%) compared with the reference group (20%) had dose decreases only. In BA16738, 7% of the patients in the Mircera group compared with 5% in the reference group had dose decreases only.

**Table 16: Patients with Dose Adjustments
Phase 3 Correction Studies (Safety Population)**

Study	R00503821 1*/2 weeks	Reference
BA16736	N= 135, n= 135	N= 46, n= 46
No Dose Change	15 (11.1%)	1 (2.2%)
Any Dose Change	120 (88.9%)	45 (97.8%)
Dose Increase(s) only	50 (37.0%)	8 (17.4%)
Dose Decrease(s) only	11 (8.1%)	9 (19.6%)
Dose Decrease(s) and Increase(s)	59 (43.7%)	28 (60.9%)
BA16738	N= 161, n= 161	N= 162, n= 162
No Dose Change	6 (3.7%)	3 (1.9%)
Any Dose Change	155 (96.3%)	159 (98.1%)
Dose Increase(s) only	21 (13.0%)	8 (4.9%)
Dose Decrease(s) only	11 (6.8%)	8 (4.9%)
Dose Decrease(s) and Increase(s)	123 (76.4%)	143 (88.3%)

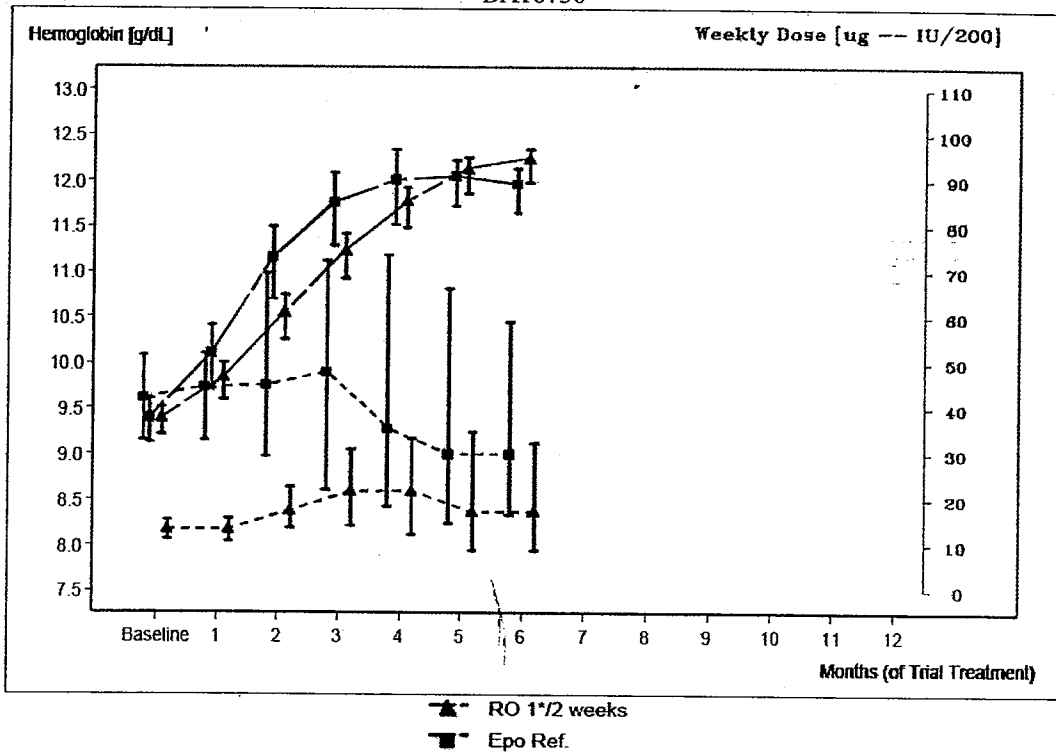
In both anemia correction studies, the median number of dose changes per patient throughout the entire study in the Mircera Q2W groups was between 3 and 5 (safety population, **Table 17**). The number of median dose changes was slightly higher in the darbepoetin/epoetin groups. Virtually identical findings were found in the PP, eligible, and ITT populations. **Figure 7** shows the mean equivalent QW dose of trial treatment and mean hemoglobin over time for both anemia correction studies.

**Table 17: Number of Dose Changes per Week per Patient
Phase 3 Correction Studies (Safety Population)**

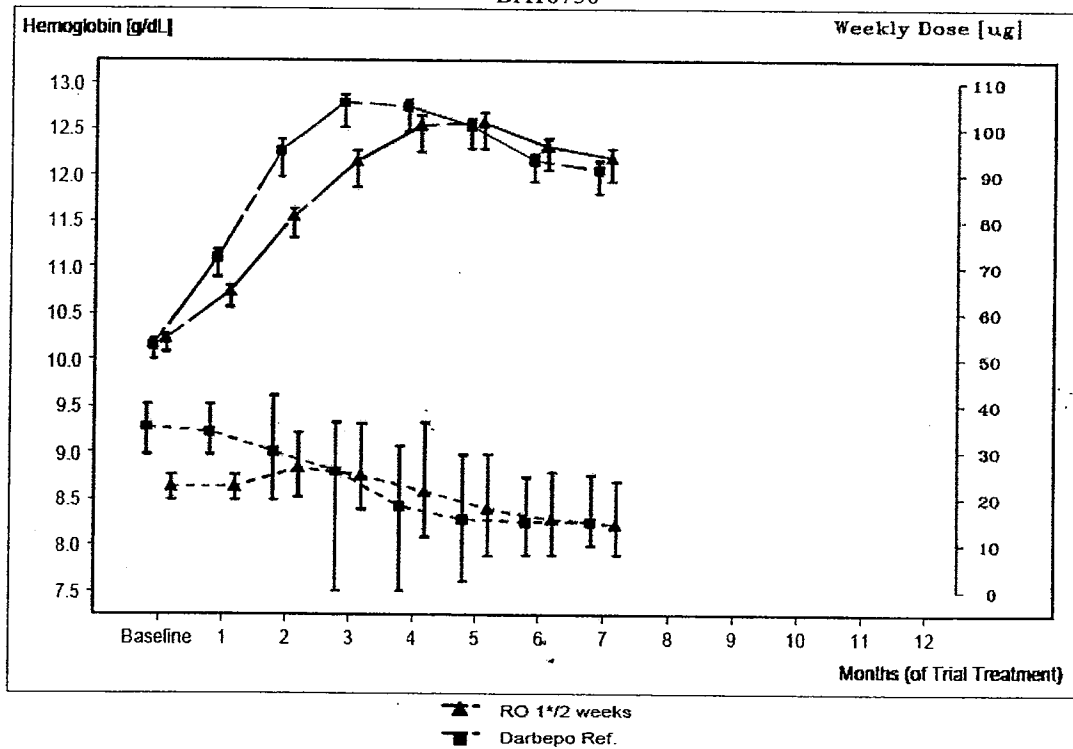
Study	Treatment		N	Mean	SD
BA16736	R00503821 1*/2 weeks	N of Any Dose Changes	135	3.12	2.29
		N of Dose Decreases	135	1.04	1.30
		N of Dose Increases	135	2.08	1.62
	Reference	N of Any Dose Changes	46	3.87	2.30
		N of Dose Decreases	46	1.96	1.43
		N of Dose Increases	46	1.91	1.70
BA16738	R00503821 1*/2 weeks	N of Any Dose Changes	161	5.45	3.25
		N of Dose Decreases	161	2.36	1.83
		N of Dose Increases	161	3.09	2.09
	Reference	N of Any Dose Changes	162	6.79	3.77
		N of Dose Decreases	162	3.48	1.99
		N of Dose Increases	162	3.31	2.15

**Figure 7: Mean Equivalent Weekly Dose and Hemoglobin Response
Phase 3 Correction Studies (ITT Population)**

BA16736



BA16738



Primary Efficacy Results

The primary parameter in both phase 3 anemia correction studies was the hemoglobin response rate, defined as an increase from baseline in hemoglobin of at least 1.0 g/dL and a hemoglobin of at least 11 g/dL, without RBC transfusion, during the anemia correction period (first 24 weeks after first dose) in BA16736, and during the anemia correction and evaluation periods (first 28 weeks after first dose) in BA16738. Values were based on QW hemoglobin measurements in BA16736 and Q2W hemoglobin measurements in BA16738.

The primary hypothesis tested was that the response rate in the Mircerca group was at least 60% (BA16736) or greater than 60% (BA16738) in the ITT population. Response rates in the Mircerca groups were far greater than 60% in both studies: 93% in BA16736 and 98% in BA16738. In addition, response rates in the Mircerca groups were comparable to those in the reference groups: 91% in BA16736 and 96% in BA16738. In all instances, the lower level of the CI interval was well above 60% with statistically significant $p < 0.0001$ (Tables 18 and 9).

**Table 18: Patients with Hemoglobin Response
Phase 3 Correction Studies (ITT Population)**

Study	Treatment	Total Number	Number of Responder	Response Rate (%)	Clopper-Pearson 95% CI		p-value
					Lower Limit	Upper Limit	
BA16736	RO0503821 1*/2 weeks	135	126	93.33	87.72	96.91	<.0001
	Reference	46	42	91.30	79.21	97.58	<.0001
BA16738	RO0503821 1*/2 weeks	162	158	97.53	93.80	99.32	<.0001
	Reference	162	156	96.30	92.11	98.63	<.0001

**Table 19: Patients with Hemoglobin Response
Phase 3 Correction Studies (PP Population)**

Study	Treatment	Total Number	Number of Responder	Response Rate (%)	Clopper-Pearson 95% CI		p-value
					Lower Limit	Upper Limit	
BA16736	RO0503821 1*/2 weeks	119	117	98.32	94.06	99.80	<.0001
	Reference	36	35	97.22	85.47	99.93	<.0001
BA16738	RO0503821 1*/2 weeks	139	138	99.28	96.06	99.98	<.0001
	Reference	144	143	99.31	96.19	99.98	<.0001

Mean Change in Hemoglobin Concentration

Study BA16738 had a second primary efficacy parameter, which was tested hierarchically: the change in average hemoglobin between baseline and the evaluation periods. In the ITT population, the median change in average hemoglobins was similar between the darbepoetin alfa and Mircera treatment groups: 2.01 g/dL, Mircera vs 1.84 g/dL, darbepoetin alfa. Mean and median values in the eligible population were the same as those in the ITT population. Similar results were seen in the PP population (Tables 20 and 21).

Table 20 Change in Hemoglobin in BA16738 (ITT Population)

Treatment	N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
RO0503821 1*/2 weeks	161	2.09	1.09	-	1.41	2.01	2.91	
Darbepoetin Reference	161	1.98	1.14	-	1.22	1.84	2.79	

Table 21 Change in Hemoglobin in BA16738 (PP Population)

Treatment	N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
RO0503821 1*/2 weeks	139	2.12	1.06	-	1.46	2.06	2.91	
Darbepoetin Reference	144	2.02	1.05	-	1.30	1.85	2.76	

An ANCOVA model was used to estimate the change in average hemoglobin between baseline and the evaluation periods in the Mircera group and darbepoetin group. A hypothesis test of non-inferiority based on this model with a non-inferiority limit of -0.75, was used to compare the groups. In all study populations, the lower limit of the CI was greater than -0.75, with p-values < 0.0001, further supporting the non-inferiority of the Mircera treatment group to the darbepoetin alfa group. Results for the ITT population are presented in Table 22. Results for the PP population are presented in Table 23. Results in the eligible population were similar to those in both the ITT and PP populations.

Table 22 Non-Inferiority Test for Treatment Differences Hemoglobin Change in Study BA16738 (ITT Population)

Treatment	RO0503821 Adj. Mean Change	Reference Adj. Mean Change	Differenc		DF	P-Value of NI Test	Lower 95% CI	Upper 95% CI
			Between Groups	Standard Error				
RO0503821 1*/2 weeks (N = 162)	2.118 (n=161)	1.949 (n=161)	0.169	0.1072	318	<.0001	-0.042	0.380

DF = degrees-of freedom

**Table 23 Non-Inferiority Test for Treatment Differences
Hemoglobin Change in Study BA16738 (PP Population)**

Treatment	R00503821 Adj. Mean Change	Reference Adj. Mean Change	Difference		DF	P-Value of NI Test	Lower 95% CI	Upper 95% CI
			Between Groups	Standard -Error				
R00503821 1*/2 weeks (N = 139)	2.152 (n=139)	1.997 (n=144)	0.155	0.1012	279	<.0001	-0.045	0.354

DF = degrees of freedom

Secondary Efficacy Results

The secondary efficacy endpoints were the hemoglobin values and their change from baseline over time, the time to target hemoglobin response, and the incidence of blood transfusion during the first 24 weeks (BA16736) or the first 28 weeks (BA16738) of the study.

Hemoglobin Concentrations and Their Changes from Baseline Over Time

Hemoglobin values over time in BA16736 and BA16738 are depicted graphically in **Figure 8** (ITT population). In both studies, median hemoglobins reached levels above 11 g/dL during the anemia correction period in all treatment groups. 11 g/dL is considered to be the lower limit of clinically acceptable hemoglobins for this patient population (patients who have anemia associated with CRF) in both NKF-KDOQI and EU practice guidelines. In both studies, the rate of increase was slower in the Mircera group than in the reference group.

For BA16736 (in dialysis patients):

- In the Mircera group the median hemoglobin value reached above 11 g/dL at month 3. During this time, median hemoglobin values increased from 9.35 g/dL to 11.19.0 g/dL with a median change of 2.00 g/dL over baseline.
- In the reference group (epoetin (alfa or beta)) the median hemoglobin value exceeded 11 g/dL at month 2. During this time, median hemoglobin values increased from 9.28 g/dL to 11.34 g/dL, with a median change of 1.82.0 g/dL over baseline.

Median hemoglobin values in the Mircera group increased through month 6 to 12.29.0 g/dL, then decreased very slightly to 12.18 g/dL by the end of the anemia correction period. Median hemoglobin values in the reference group continued to increase through month 4 to 12.08 g/dL, then decreased slightly but remained above 11 g/dL through to the end of the anemia correction period (**Figure 8**). Decreases were due primarily to dose adjustments.

For BA16738 (in patients not on dialysis):

- In the Mircera group the median hemoglobin value exceeded 11 g/dL at month 2. Median hemoglobin values increased from 10.37 g/dL to 11.60 g/dL with a median change of 1.32.0 g/dL over baseline.
- In the reference group (darbepoetin alfa) the median hemoglobin value exceeded 11 g/dL at month 1. Median hemoglobin values increased from 10.33 g/dL to 11.20 g/dL, with a median change of 0.94 g/dL over baseline. Median hemoglobin values in the Mircera group increased through month 5 to 12.75 g/dL, then decreased slightly to 12.20 g/dL by the end of the evaluation period. Decreases were due primarily to dose adjustments.

In the reference group, median hemoglobin values continued to increase through month 3 to 12.80 g/dL, then decreased slightly but remained above 11 g/dL until the end of the evaluation period (Figure 8). Plots of the change from baseline over time in hemoglobin values in the ITT population are presented in Figure 9.

**Figure 8: Median Hemoglobin over Time
Phase 3 Correction Studies (ITT Population)**

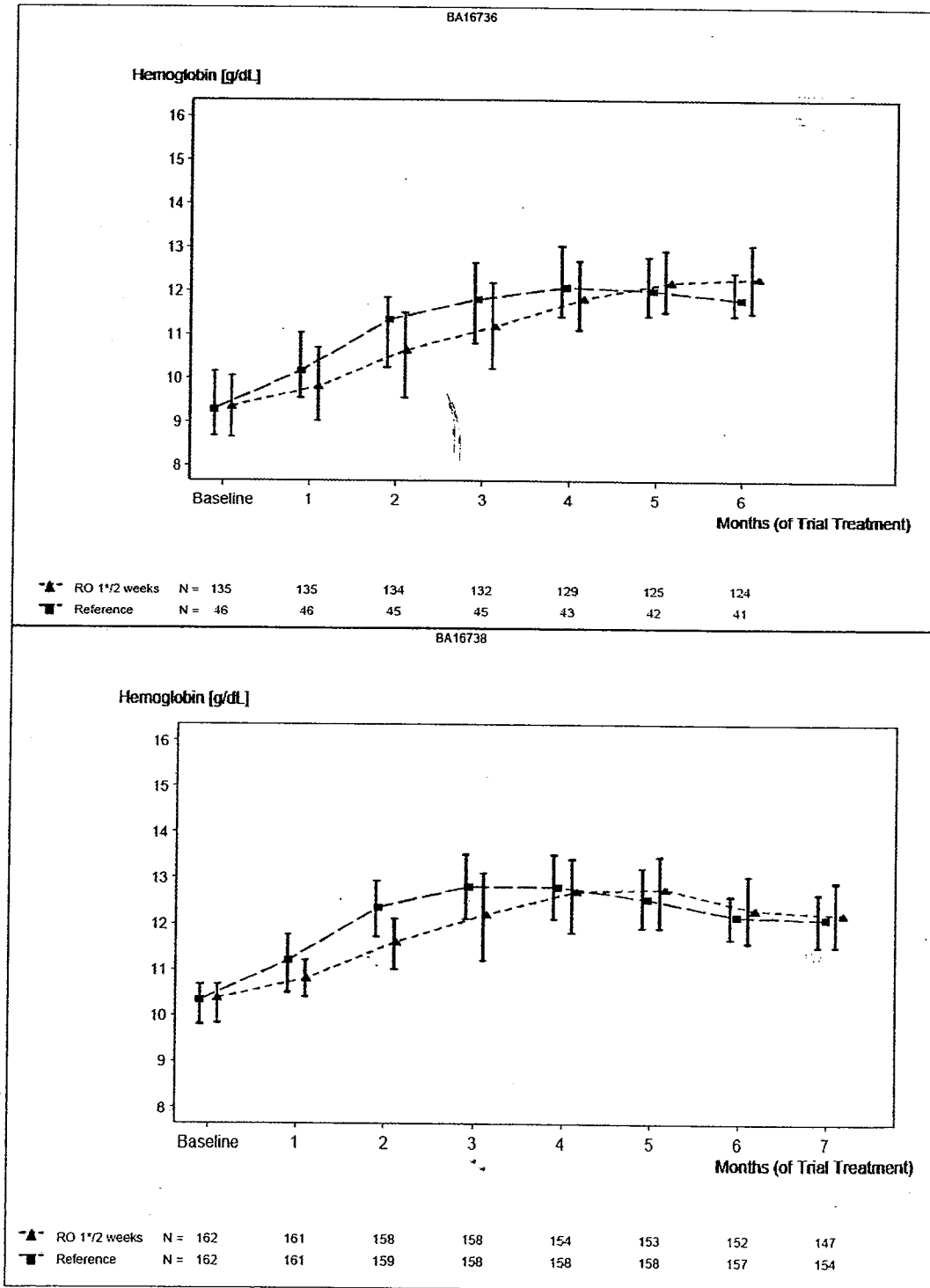
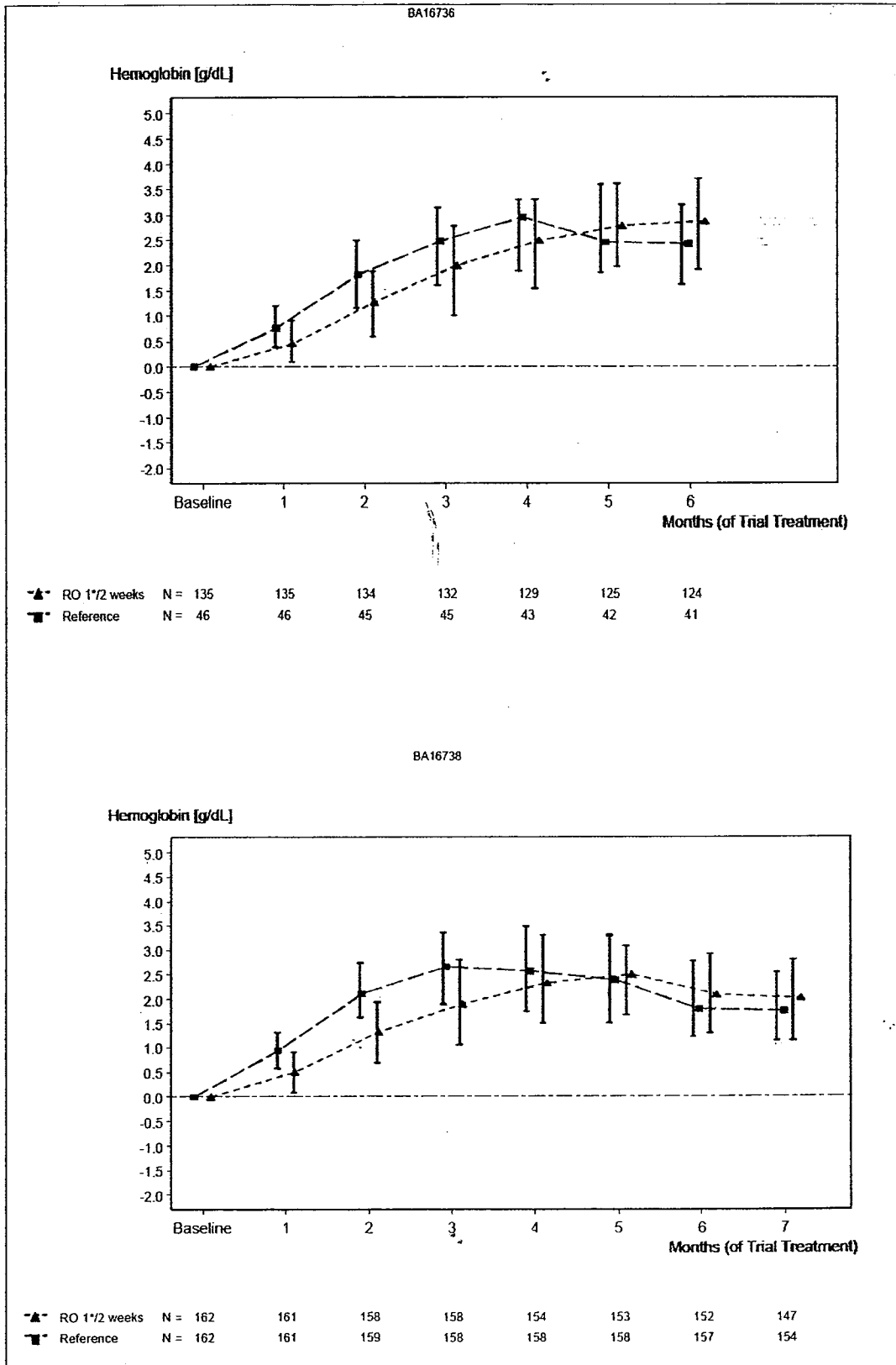


**Figure 9: Median Change in Hemoglobin over Time
Phase 3 Correction Studies (ITT Population)**



Hemoglobin Values over 13 and 14 g/dL

A summary showing the proportions of patients with maximum hemoglobin values > 13 g/dL by month is provided in Table 24. The percentage of patients reaching maximum hemoglobin values > 13 g/dL was higher during the first 4 months in the reference group compared with the Mircera group in both studies. In the Mircera groups, the highest proportion of patients with hemoglobin > 13 g/dL was at month 5, whereas the highest percentages in the reference groups were at month 3 and 4 in BA16738 and at month 5 in BA16736. These results are consistent with the change from baseline over time in hemoglobins and the slower time to target hemoglobin response seen in the Mircera groups. A similar pattern was seen in the proportion of patients with maximum hemoglobin values > 14.0 g/dL by month (Table 25).

**Table 24: Hemoglobin Values over 13 g/dL by Month
Phase 3 Correction Studies (ITT Population)**

Treatment		Month		Patients with max Hb value					
				≤ 13 g/dL		> 13 g/dL		All	
				N	%	N	%	N	%
RO0503821 1* / 2 weeks BA16736	1	133	98.52	2	1.48	135	100.00		
	2	124	92.54	10	7.46	134	100.00		
	3	106	80.30	26	19.70	132	100.00		
	4	85	65.89	44	34.11	129	100.00		
	5	72	57.60	53	42.40	125	100.00		
	6	75	60.48	49	39.52	124	100.00		
Epoetin Reference BA16736	1	45	97.83	1	2.17	46	100.00		
	2	37	82.22	8	17.78	45	100.00		
	3	31	68.89	14	31.11	45	100.00		
	4	28	65.12	15	34.88	43	100.00		
	5	26	61.90	16	38.10	42	100.00		
	6	34	82.93	7	17.07	41	100.00		
Treatment		Month		Patients with max Hb value					
				≤ 13 g/dL		> 13 g/dL		All	
				N	%	N	%	N	%
RO0503821 1* / 2 weeks BA16738	1	158	98.14	3	1.86	161	100.00		
	2	140	88.61	18	11.39	158	100.00		
	3	108	68.35	50	31.65	158	100.00		
	4	81	52.60	73	47.40	154	100.00		
	5	81	52.94	72	47.06	153	100.00		
	6	97	63.82	55	36.18	152	100.00		
	7	111	75.51	36	24.49	147	100.00		
Darbepoetin Reference BA16738	1	149	92.55	12	7.45	161	100.00		
	2	105	66.04	54	33.96	159	100.00		
	3	71	44.94	87	55.06	158	100.00		
	4	73	46.20	85	53.80	158	100.00		
	5	86	54.43	72	45.57	158	100.00		
	6	113	71.97	44	28.03	157	100.00		
	7	129	83.77	25	16.23	154	100.00		

**Table 25: Hemoglobin Values over 14 g/dL by Month
Phase 3 Correction Studies (ITT Population)**

Treatment	Month	Patients with max Hb value > 14 g/dL		All	
		N	%	N	%
RO0503821 1*/2 weeks BA16738	1	.	.	161	100.00
	2	5	3.16	158	100.00
	3	18	11.39	158	100.00
	4	25	16.23	154	100.00
	5	25	16.34	153	100.00
	6	15	9.87	152	100.00
	7	7	4.76	147	100.00
Darbepoetin Reference BA16738	1	.	.	161	100.00
	2	20	12.58	159	100.00
	3	36	22.78	158	100.00
	4	33	20.89	158	100.00
	5	20	12.66	158	100.00
	6	12	7.64	157	100.00
	7	7	4.55	154	100.00
Treatment	Month	Patients with max Hb value > 14 g/dL		All	
		N	%	N	%
RO0503821 1*/2 weeks BA16736	1	1	0.74	135	100.00
	2	4	2.99	134	100.00
	3	7	5.30	132	100.00
	4	7	5.43	129	100.00
	5	15	12.00	125	100.00
	6	8	6.45	124	100.00
Epoetin Reference BA16736	1	.	.	46	100.00
	2	2	4.44	45	100.00
	3	4	8.89	45	100.00
	4	5	11.63	43	100.00
	5	2	4.76	42	100.00
	6	.	.	41	100.00

Time to Target Hemoglobin Response

In each anemia correction study, the median time to target hemoglobin response was longer in the Mircera group than in the reference group. In BA16736 this took 57 days (8.1 weeks, Mircera) vs 31 days (4.5 weeks, epoetin (alfa or beta)), and in BA16738 this took 43 days (6.1 weeks,

Mircera) vs 29 days (4.1 weeks, darbepoetin alfa). In both studies, the difference was statistically significant $p < 0.0001$ (Table 26).

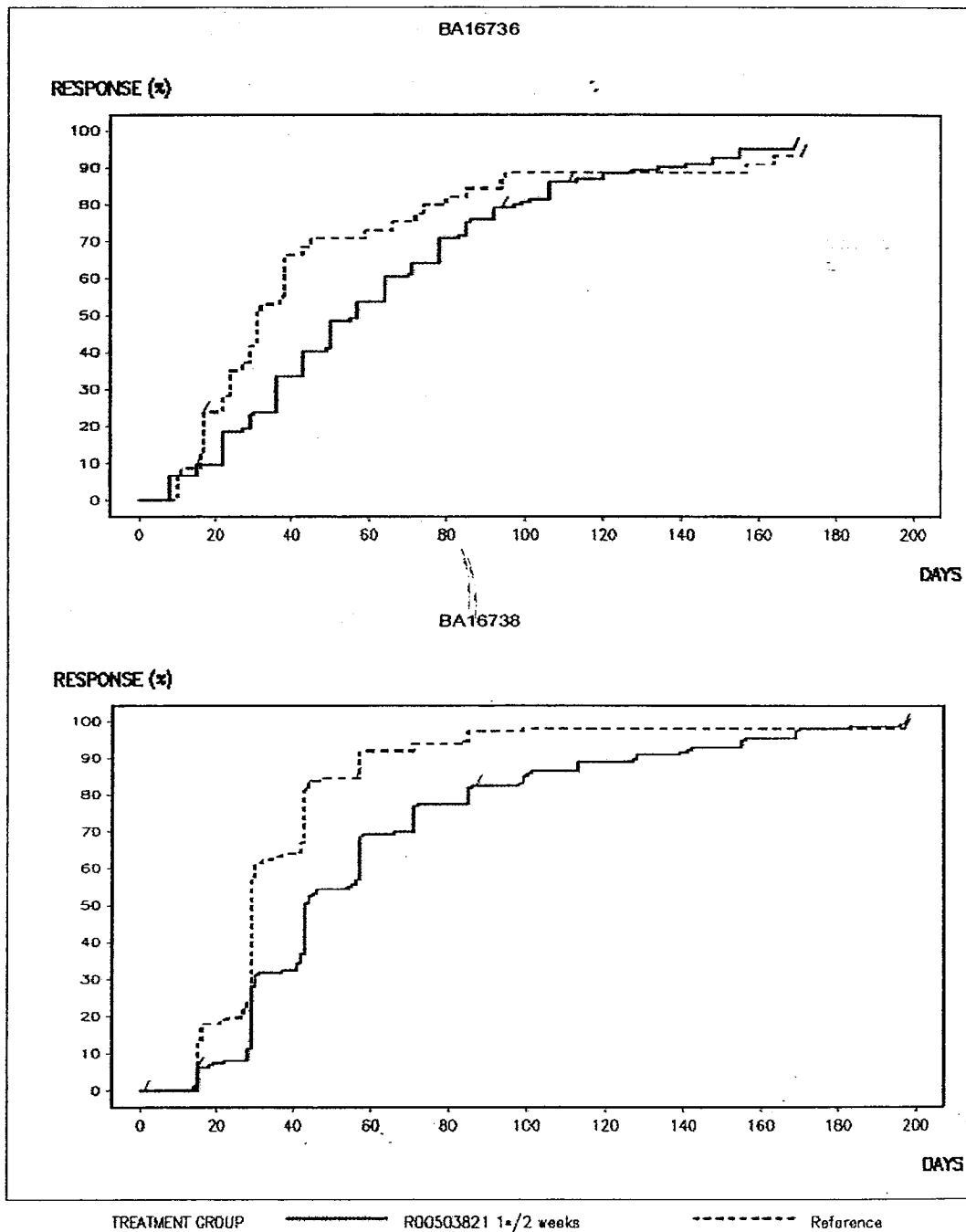
These data were similar in both the PP population and the eligible population. Patients in the Mircera groups did reach the same hemoglobins as in the reference groups, but at a slower rate (Figure 10). Kaplan-Meier plots of responders showed a similar difference in the time to response between treatment groups when analyzed in the PP population and in the eligible population.

**Table 26: Time to Hemoglobin Response
Phase 3 Correction Studies (ITT Population)**

Study	Treatment	Statistic	Value	
BA16736	R00503821 1*/2 weeks	Number of Patients	135	
		Number of Responders	126 (93.33%)	
		Censored	9 (6.67%)	
		Median Time to Response 95% CI	57.00 50.00 - 64.00	
	Reference	Number of Patients	46	
		Number of Responders	42 (91.30%)	
		Censored	4 (8.70%)	
		Median Time to Response 95% CI	31.00 27.00 - 38.00	
	BA16738	R00503821 1*/2 weeks	Number of Patients	162
			Number of Responders	158 (97.53%)
Censored			4 (2.47%)	
Median Time to Response 95% CI			43.00 43.00 - 57.00	
Reference		Number of Patients	162	
		Number of Responders	156 (96.30%)	
		Censored	6 (3.70%)	
		Median Time to Response 95% CI	29.00 -	
Log-rank p-value: <.0001				

Hemoglobin response was defined as an increase in hemoglobin of at least 1 g/dL above baseline with an absolute concentration of 11 g/dL or above during correction/evaluation period without RBC transfusion (through day 173 in BA16736; through day 201 in BA16738)

**Figure 10: Kaplan-Meier Plot of Responders
Phase 3 Correction Studies (ITT Population)**



RBC Transfusions

Since blood transfusions are used as treatment for severe anemia, they are considered a measure of treatment efficacy rather than of treatment safety. The percentage of patients in the safety population who required blood transfusions during the anemia correction period was similar between treatment groups within each anemia correction study: 5% of patients in the Mircera group vs 4% of patients in the reference group in BA16736, and 3% of patients in the Mircera

group vs 7% of patients in the reference group in BA16738. These data are shown for the safety population in **Table 27**.

The percentage of patients who required blood transfusions for AE was similar between treatment groups in both anemia correction studies. The results are the same in the ITT population and similar in the eligible population. Fewer patients required blood transfusions in the PP population, due to the nature of the population. In BA16736 patients with blood transfusions during weeks 1 to 24 were excluded from the PP population. In BA16738, patients with blood transfusions during weeks 1 to 28 were excluded from the PP population. However, patients receiving blood transfusions for loss of effect were not excluded from the PP population of either study. The percentage of patients with blood transfusions during the anemia correction period (BA16736) or evaluation and anemia correction period (BA16738) was similar between treatment groups within each study: less than 2% of patients in any treatment group (no more than 2 patients per group).

Table 27: Blood Transfusions in Phase 3 Correction Studies (Safety Population)

Study	Treatment	All Blood Transfusion			Units Transfused		Blood Transfusions for AEs					
		Total Pts with at Least one BT		Total Number of BTs	Mean BTs per patient	Mean Units per BT	Median Units per BT	Total Pts with at Least one BT		Total Number of BTs		
		N	(%)	N	(%)			N	(%)	N	(%)	
BA16736	RO0503821 1*/2 weeks (N = 135)	7	(5.2%)	8	(47.1%)	1.14	1.75	1.50	5	(3.7%)	6	(42.9%)
	Reference (N = 46)	2	(4.3%)	9	(52.9%)	4.50	1.78	1.00	2	(4.3%)	8	(57.1%)
BA16738	RO0503821 1*/2 weeks (N = 161)	4	(2.5%)	6	(20.0%)	1.50	2.17	1.00	4	(2.5%)	6	(21.4%)
	Reference (N = 162)	11	(6.8%)	24	(80.0%)	2.18	1.63	2.00	10	(6.2%)	22	(78.6%)

Summary of Efficacy Results and Dosing Conclusions: Anemia Correction

- Study BA16736 was in patients with CRF receiving dialysis treatment. The starting dose of Mircera was 0.4 ug/kg administered IV every 2 weeks.
 - The response rate in the Mircera group at the end of the anemia correction period was 93% ($p < 0.0001$; 95% CI 87.7-96.9); and the lower limit of the CI was well above 60%, confirming that Mircera resulted in the anemia correction of anemia.
 - The time to response data indicated that the anemia correction of anemia was slower in the Mircera group compared with the epoetin group (median time to response was 57 days in the Mircera group and 31 days in the epoetin group).
 - Majority of patients in both treatment arms had dose adjustments (90% and 98% of patients in the Mircera and epoetin groups, respectively). At the time of hemoglobin response, with dose adjustments, the median dose of Mircera was 0.6 ug/kg/2-wk and the median dose in the epoetin group was similar to the median starting dose.
 - These results indicate that the dosing regimen (Mircera 0.4 ug/kg/2-wk) was effective as tested, but dose optimization could be considered. Subgroup analysis by age, weight, gender,

race, ethnicity, geographic region, CRF etiology, and diabetes revealed no significant difference in hemoglobin response.

- Study BA16738 was in patients with CRF who did not require dialysis treatment. The starting dose of Mircerca was 0.6 ug/kg administered SC every 2 weeks.
 - The response rate in the Mircerca group during the anemia correction and evaluation periods was similar to that seen in BA16736, 98% ($p < 0.0001$; 95% CI 93.8-99.3%) with the lower limit of the CI well above 60%, confirming that Mircerca resulted in anemia correction of anemia.
 - An ANCOVA showed that the adjusted mean change from baseline hemoglobin in the Mircerca group (2.18 g/dL) was not inferior to that of the darbepoetin alfa reference group (1.95 g/dL), in the ITT population. The results were consistent in the PP, ITT, and eligible populations ($p < 0.0001$).
 - Time to response and hemoglobin over time data indicated that the anemia correction of anemia was slower in the Mircerca group compared with the darbepoetin alfa group. The median time to response was 43 days (approximately 6 weeks) in the Mircerca group compared with 29 days (approximately 4 weeks) in the darbepoetin alfa group.
 - The rate of hemoglobin increase observed in the Mircerca group appeared appropriate in this patient population, since a high response rate was achieved (98%) without an increased incidence of AE, serious adverse events (SAE), withdrawals due to AE, or RBC transfusions.
 - Fewer patients in the Mircerca group reached a maximum hemoglobin value > 14.0 g/dL during the first 4 months of the study than in the reference group.
 - These results indicate that the dosing regimen (Mircerca 0.6 ug/kg/2-wk SC) was effective as tested. Subgroup analysis by age, weight, gender, race, ethnicity, geographic region, CRF etiology, and diabetes revealed no significant difference in hemoglobin response.

Hemoglobin Maintenance

Study Populations Overview

A total of 1894 patients were randomized into the phase 3 hemoglobin maintenance studies. The number of patients to enter and complete the studies is presented in **Table 28**.

Table 28: Patient Disposition (Phase 3 Hemoglobin Maintenance Studies)

Maintenance Studies	Randomized	Completed the Titration Period	Completed the Evaluation Period	Completed the Safety Follow-up
BA16739				
RO0503821 1x/2 wk	223	197	190	169
RO0503821 1x/4 wk	224	188	183	168
Reference	226	205	199	180
BA16740				
RO0503821 1x/2 wk	190	164	161	154
RO0503821 1x/4 wk	191	170	166	148
Reference	191	181	175	159
BA17283				
RO0503821 1x/2 wk	157	139	130	118
Reference	156	143	136	131
BA17284				
RO0503821 1x/2 wk	168	146	132	N/A
Reference	168	160	150	N/A

Overall, approximately 61% (1153/1894) of the enrolled patients were randomized to receive Mircera, and 39% (741/1894) were randomized to receive a reference medication. The overall 2:1 randomization ratio (by study agent) resulted from having two Mircera arms in BA16739 and BA16740 (Mircera Q2W, Mircera Q4W, reference agent). The randomization ratio in all studies was 1:1 by study arms. A breakdown of the study population by route of administration, mode of dialysis, administration regimen, and geographical region is provided in Table 29.

Table 29: Study Populations in Phase 3 Maintenance Studies

	BA16739			BA16740			BA17283		BA17284	
	RO0503821 1*/2 weeks (N =223)	RO0503821 1*/4 weeks (N =224)	Reference (N =226)	RO0503821 1*/2 weeks (N =190)	RO0503821 1*/4 weeks (N =191)	Reference (N =191)	RO0503821 1*/2 weeks (N =157)	Reference (N =156)	RO0503821 1*/2 weeks (N =168)	Reference (N =168)
Route of Study Drug Administration										
IV	223 (100.0%)	224 (100.0%)	226 (100.0%)				157 (100.0%)	156 (100.0%)	113 (67.3%)	114 (67.9%)
SC				190 (100.0%)	191 (100.0%)	191 (100.0%)			55 (32.7%)	54 (32.1%)
Mode of Current Dialysis										
Hemodialysis	223 (100.0%)	224 (100.0%)	226 (100.0%)	176 (92.6%)	177 (92.7%)	171 (89.5%)	157 (100.0%)	155 (99.4%)	159 (94.6%)	158 (94.0%)
Peritoneal Dialysis				14 (7.4%)	14 (7.3%)	20 (10.5%)		1 (0.6%)	9 (5.4%)	10 (6.0%)
Schedule of Study Drug Administration										
<=1*/week			225 (99.6%)			191 (100.0%)	1 (0.6%)	130 (83.3%)		168 (100.0%)
1*/2 weeks	223 (100.0%)			190 (100.0%)			156 (99.4%)	26 (16.7%)	168 (100.0%)	
1*/4 weeks		224 (100.0%)			191 (100.0%)					
Not Available*			1 (0.4%)							
Geographical Region										
USA	151 (67.7%)	152 (67.9%)	152 (67.3%)	22 (11.6%)	23 (12.0%)	23 (12.0%)			96 (57.1%)	93 (55.4%)
non-USA	72 (32.3%)	72 (32.1%)	74 (32.7%)	168 (88.4%)	168 (88.0%)	168 (88.0%)	157 (100.0%)	156 (100.0%)	72 (42.9%)	75 (44.6%)

* Patients in epoetin alfa or beta reference arm, who did not enter treatment period

Patient Withdrawals

An analysis of withdrawals in the ITT population is presented in Table 30. A total of 383 patients in the ITT population were withdrawn prematurely. Generally, withdrawal rates between treatment groups within a study were comparable (i.e., within approximately 5% of each other).

- Differences in withdrawal rates in the range of 9% to 10% were seen in BA17283 and BA17284, only. These differences were due primarily to a higher percentage of withdrawals for non-safety reasons in the Mircera groups:
 - In BA17283, 17% of patients in the Mircera group were withdrawn for non-safety reasons compared to 9% in the reference group
 - In BA17284, 15% of patients in the Mircera group were withdrawn for non-safety reasons compared to 5% in the reference group.
- In all studies, most premature withdrawals were for non-safety reasons. Non-safety reasons included insufficient therapeutic response, refused treatment/withdrew consent, failure to return,

and “other.” The majority of patients withdrawn for non-safety reasons were withdrawn for reasons categorized as “other.” The main reason for withdrawal in the “other” category was kidney transplantation, which occurred as follows:

- 13 patients (6%) in the Mircera Q2W, 16 patients (7%) in the Mircera Q4W, and 11 patients (5%) in the reference group of BA16739.
- 14 patients (7%) in the Mircera Q2W, 11 patients (6%) in the Mircera Q4W, and 14 patients (7%) in the reference group of BA16740.
- 14 patients (9%) in the Mircera group and 6 patients (4%) in the reference group of BA17283.
- 13 patients (8%) in the Mircera group and 3 patients (2%) in the reference group of BA17284.

Table 30: Withdrawals in the Maintenance Studies (ITT Population)

	BA16739		BA16740		BA17283		BA17284			
	RO0503821 1*/2 weeks (N =223)	RO0503821 1*/4 weeks (N =224)	Reference (N =226)	RO0503821 1*/2 weeks (N =190)	RO0503821 1*/4 weeks (N =191)	Reference (N =191)	RO0503821 1*/2 weeks (N =157)	Reference (N =156)	RO0503821 1*/2 weeks (N =168)	Reference (N =168)
Safety	26 (11.7%)	20 (8.9%)	14 (6.2%)	13 (6.8%)	18 (9.4%)	12 (6.3%)	13 (8.3%)	11 (7.1%)	11 (6.5%)	9 (5.4%)
Abnormality of Laboratory Test	0	0	0	0	0	0	0	0	0	0
Adverse Event (a)	9 (4.0%)	7 (3.1%)	1 (0.4%)	1 (0.5%)	0	1 (0.5%)	1 (0.6%)	1 (0.6%)	4 (2.4%)	0
Death	17 (7.6%)	13 (5.8%)	13 (5.8%)	12 (6.3%)	18 (9.4%)	11 (5.8%)	12 (7.6%)	10 (6.4%)	7 (4.2%)	9 (5.4%)
Non-Safety	28 (12.6%)	36 (16.1%)	32 (14.2%)	21 (11.1%)	25 (13.1%)	20 (10.5%)	26 (16.6%)	14 (9.0%)	25 (14.9%)	9 (5.4%)
Insufficient Therapeutic Response	1 (0.4%)	0	0	2 (1.1%)	0	0	0	0	1 (0.6%)	0
Early Improvement	0	0	0	0	0	0	0	0	0	0
Violation of Selection Criteria at Entry	0	0	0	0	0	0	0	0	0	0
Other Protocol Violation	0	0	0	0	0	0	0	0	0	0
Refused Treatment (b)	4 (1.8%)	10 (4.5%)	6 (2.7%)	2 (1.1%)	10 (5.2%)	1 (0.5%)	4 (2.5%)	3 (1.9%)	4 (2.4%)	0
Failure to Return	0	1 (0.4%)	2 (0.9%)	1 (0.5%)	0	0	2 (1.3%)	0	0	1 (0.6%)
Other	23 (10.3%)	25 (11.2%)	24 (10.6%)	16 (8.4%)	15 (7.9%)	19 (9.9%)	20 (12.7%)	11 (7.1%)	20 (11.9%)	3 (4.0%)
Total	54 (24.2%)	56 (25.0%)	46 (20.4%)	34 (17.9%)	43 (22.5%)	32 (16.8%)	39 (24.8%)	25 (16.0%)	36 (21.4%)	18 (10.7%)

(a) = including intercurrent illness; (b) = including "did not cooperate" and "withdrew consent"

Analysis Populations

The populations defined for analysis of the phase 3 efficacy endpoints included the ITT, PP, and eligible populations. Discussions of the primary efficacy analyses focus on the PP population, because the PP population is considered the more conservative population for non-inferiority testing. However, results were consistent between the ITT, PP and eligible population in all cases. Discussions of the secondary efficacy analyses focus on the ITT population. The percentages of patients included in the ITT, safety, and eligible populations in each of the studies

were well balanced across treatment groups. An overview of the number and percentage of patients in the different populations is provided in **Table 31**.

Table 31: Analysis Populations in Phase 3 Maintenance Studies

Analysis Population	BA16739			BA16740			BA17283		BA17284	
	FO0503821 1* /2 weeks	FO0503821 1* /4 weeks	Reference	FO0503821 1* /2 weeks	FO0503821 1* /4 weeks	Reference	FO0503821 1* /2 weeks	Reference	FO0503821 1* /2 weeks	Reference
All Patients	223 (100.0%)	224 (100.0%)	226 (100.0%)	190 (100.0%)	191 (100.0%)	191 (100.0%)	157 (100.0%)	156 (100.0%)	168 (100.0%)	168 (100.0%)
Intent to Treat	223 (100.0%)	224 (100.0%)	226 (100.0%)	190 (100.0%)	191 (100.0%)	191 (100.0%)	157 (100.0%)	156 (100.0%)	168 (100.0%)	168 (100.0%)
Safety	221 (99.1%)	220 (98.2%)	225 (99.6%)	190 (100.0%)	190 (99.5%)	191 (100.0%)	153 (97.5%)	156 (100.0%)	165 (98.2%)	168 (100.0%)
Eligible	220 (98.7%)	216 (96.4%)	222 (98.2%)	187 (98.4%)	189 (99.0%)	191 (100.0%)	153 (97.5%)	154 (98.7%)	158 (94.0%)	161 (95.8%)
Per Protocol	188 (84.3%)	172 (76.8%)	180 (79.6%)	154 (81.1%)	153 (80.1%)	167 (87.4%)	123 (78.3%)	126 (80.8%)	123 (73.2%)	133 (79.2%)

Baseline Demographic Characteristics

Demographic characteristics were generally similar among treatment groups within each of the studies. Slight imbalances were seen in gender distribution in BA17283 (Mircera group was 64% male compared with 52% in the reference group), and race distribution in BA17284 (Mircera group was 62% Caucasians compared with 52% in the reference group). Studies with a large percentage of US patients (BA16739 and BA17284) generally had demographic profiles similar to each other, as did studies run primarily in non-US patients (BA16740 and BA17283). Baseline demographic characteristics are presented in **Table 32**.

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Table 32: Demographic Data, Maintenance Studies (ITT Population)

	BA16739			BA16740			BA17283			BA17284	
	RO0503821 1* /2 weeks (N =223)	RO0503821 1* /4 weeks (N =224)	Reference (N =226)	RO0503821 1* /2 weeks (N =190)	RO0503821 1* /4 weeks (N =191)	Reference (N =191)	RO0503821 1* /2 weeks (N =157)	Reference (N =156)	RO0503821 1* /2 weeks (N =168)	Reference (N =168)	
Gender											
Female	90 (40.4%)	98 (43.8%)	92 (40.7%)	82 (43.2%)	74 (39.7%)	81 (42.4%)	57 (36.3%)	75 (48.1%)	64 (38.1%)	55 (32.7%)	
Male	133 (59.6%)	126 (56.3%)	134 (59.3%)	108 (56.8%)	117 (61.3%)	110 (57.6%)	100 (63.7%)	81 (51.9%)	104 (61.9%)	113 (67.3%)	
Race											
Black	74 (33.2%)	82 (36.6%)	82 (36.3%)	13 (6.8%)	15 (7.9%)	17 (8.9%)	5 (3.2%)	4 (2.6%)	49 (29.2%)	57 (33.9%)	
Caucasian	140 (62.8%)	131 (58.5%)	133 (58.8%)	155 (81.6%)	156 (81.7%)	148 (77.5%)	143 (91.1%)	144 (92.3%)	104 (61.9%)	87 (51.0%)	
Oriental	9 (4.0%)	7 (3.1%)	11 (4.9%)	15 (7.9%)	16 (8.4%)	19 (9.9%)	4 (2.5%)	5 (3.2%)	10 (6.0%)	13 (7.7%)	
Other		4 (1.8%)		7 (3.7%)	4 (2.1%)	7 (3.7%)	5 (3.2%)	3 (1.9%)	5 (3.0%)	11 (6.5%)	
Ethnicity											
Hispanic	33 (14.8%)	30 (13.4%)	30 (13.3%)	15 (7.9%)	17 (8.9%)	19 (9.9%)	4 (2.5%)	2 (1.3%)	15 (8.9%)	11 (6.5%)	
Non-Hispanic	190 (85.2%)	194 (86.6%)	196 (86.7%)	175 (92.1%)	174 (91.1%)	172 (90.1%)	153 (97.5%)	154 (98.7%)	153 (91.1%)	157 (93.5%)	
Age [Years]											
N	223	224	226	190	191	191	157	156	168	168	
Mean	59.0	59.0	58.6	60.5	62.3	60.4	62.4	61.8	59.8	60.1	
Std. Dev.	15.20	14.99	15.13	15.40	15.36	14.70	16.17	14.74	14.38	13.95	
Median	61.0	60.0	60.5	63.0	65.0	61.0	65.0	64.0	60.0	60.0	
Min-Max	24 - 88	23 - 89	23 - 89	25 - 84	20 - 92	24 - 88	23 - 88	26 - 87	19 - 87	22 - 92	
Age Category [Years]											
<65	134 (60.1%)	134 (59.8%)	141 (62.4%)	103 (54.2%)	94 (49.2%)	107 (56.0%)	76 (48.4%)	79 (50.6%)	104 (61.9%)	104 (61.9%)	
65-74	47 (21.1%)	52 (23.2%)	50 (22.1%)	46 (24.2%)	49 (25.7%)	43 (22.5%)	39 (24.8%)	41 (26.3%)	37 (22.0%)	34 (20.2%)	
>=75	42 (18.8%)	38 (17.0%)	35 (15.5%)	41 (21.6%)	48 (25.1%)	41 (21.5%)	42 (26.8%)	36 (23.1%)	27 (16.1%)	30 (17.9%)	
Body Weight [kg]											
N	223	224	226	190	191	191	157	156	167	167	
Mean	77.2	77.6	80.6	70.8	69.0	69.3	68.9	70.3	75.5	77.4	
Std. Dev.	19.70	18.84	22.03	15.66	14.89	15.75	16.69	16.50	19.73	19.71	
Median	73.7	75.4	75.7	70.1	68.5	68.2	66.9	69.0	72.0	73.4	
Min-Max	36 -132	37 -132	47 -164	40 -129	38 -115	38 -123	37 -147	34 -126	38 -128	39 -135	
Body Weight Category [kg]											
<65	70 (31.4%)	55 (24.6%)	52 (23.0%)	75 (39.5%)	71 (37.2%)	75 (39.3%)	70 (44.6%)	64 (41.0%)	56 (33.3%)	45 (26.9%)	
65-<80	68 (30.5%)	83 (37.1%)	81 (35.8%)	74 (38.9%)	80 (41.9%)	73 (38.2%)	57 (36.3%)	56 (35.9%)	49 (29.2%)	56 (33.3%)	
>=80	85 (38.1%)	86 (38.4%)	93 (41.2%)	41 (21.6%)	40 (20.9%)	43 (22.5%)	30 (19.1%)	36 (23.1%)	62 (36.9%)	66 (39.3%)	

Baseline Disease Characteristics

Baseline parameters used to characterize the patients' disease status included primary etiology of renal failure, dialysis types and parameters, previous erythropoietins, previous and concomitant iron supplementation, and iron parameters. The disease characteristics of the patients were representative of the end-stage-renal-disease patient population in the US and in European countries. The significantly higher number of patients receiving hemodialysis compared to those receiving peritoneal dialysis is also representative of the current trends in the US. The relatively high usage of arteriovenous fistulae for dialysis access is consistent with current trends in European countries, while there is a much lower usage of arteriovenous fistulae in the US.

Baseline Disease and Treatment Status

The disease characteristics of the patients were largely influenced by the geographic location of the studies (i.e., US vs non-US). As in anemia correction studies, the most common primary

causes of renal failure across the studies were diabetes, hypertension/large vessel disease, and glomerulonephritis. Baseline disease and treatment status are presented in **Table 33**, and baseline dialysis parameters are presented for the hemoglobin maintenance studies in **Table 34**.

- In studies with a high percentage of US patients (US studies, BA16739 and BA17284), diabetes and hypertension were listed as primary causes for renal failure in a higher percentage of patients than in studies conducted mainly in non-US patients (non-US studies, BA16740 and BA17283): 34% to 44 vs 22% to 26% (diabetes) and 44% to 48 vs 19% to 28% (hypertension) of patients, respectively.
- In non-US studies, glomerulonephritis was listed as a primary cause of renal failure in a slightly higher percentage of patients than in US studies: 18% to 25% compared with 13% to 23%, respectively. In general, the most common primary causes of renal failure (diabetes, hypertension/large vessel disease, and glomerulonephritis) were distributed similarly among treatment groups within each study. Exceptions were:
 - Diabetes in BA16739 (41% Mircera Q2W, 34% Mircera Q4W, and 44% reference), and glomerulonephritis in BA17284 (23% Mircera and 17% reference).
 - Interstitial nephritis in BA17283 was a primary cause of renal failure in 16% of patients in the reference group compared with 8% of patients in the Mircera group.

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Table 33: Disease and Treatment at Baseline (Phase 3 Maintenance, ITT Population)

	BA16739			BA16740			BA17283		BA17284	
	RO0503821 1 1/2 weeks (N =223)	RO0503821 1 1/4 weeks (N =224)	Reference (N =226)	RO0503821 1 1/2 weeks (N =190)	RO0503821 1 1/4 weeks (N =191)	Reference (N =191)	RO0503821 1 1/2 weeks (N =157)	Reference (N =156)	RO0503821 1 1/2 weeks (N =168)	Reference (N =168)
Primary Cause(s) of Renal Failure										
Diabetes	91 (40.8%)	77 (34.4%)	100 (44.2%)	48 (25.3%)	44 (23.0%)	50 (26.2%)	40 (25.5%)	35 (22.4%)	60 (35.7%)	61 (36.3%)
Glomerulonephritis	37 (16.6%)	36 (16.1%)	30 (13.3%)	43 (22.6%)	42 (22.0%)	35 (18.3%)	39 (24.8%)	33 (21.2%)	39 (23.2%)	28 (16.7%)
Secondary Glomerulonephritis / Vasculitis	3 (1.3%)	6 (2.7%)	6 (2.7%)	3 (1.6%)	8 (4.2%)	7 (3.7%)	9 (5.7%)	10 (6.4%)	5 (3.0%)	2 (1.2%)
Interstitial nephritis / Pyelonephritis	13 (5.8%)	9 (4.0%)	12 (5.3%)	23 (12.1%)	29 (15.2%)	30 (15.7%)	13 (8.3%)	25 (16.0%)	7 (4.2%)	13 (7.7%)
Hypertension / large vessel disease	99 (44.4%)	104 (46.4%)	107 (47.3%)	53 (27.9%)	52 (27.2%)	54 (28.3%)	37 (23.6%)	30 (19.2%)	73 (43.5%)	81 (48.2%)
Polycystic kidney disease/ (adult type, dominant)	8 (3.6%)	10 (4.5%)	10 (4.4%)	11 (5.8%)	8 (4.2%)	16 (8.4%)	7 (4.5%)	8 (5.1%)	7 (4.2%)	7 (4.2%)
Other hereditary / Congenital diseases	3 (1.3%)	8 (3.6%)	4 (1.8%)	5 (2.6%)		3 (1.6%)	8 (5.1%)	1 (0.6%)	5 (3.0%)	6 (3.6%)
Neoplasms / tumors	2 (0.9%)	5 (2.2%)	5 (2.2%)	2 (1.1%)	2 (1.0%)	4 (2.1%)	2 (1.3%)	1 (0.6%)	4 (2.4%)	3 (1.8%)
Other	9 (4.0%)	12 (5.4%)	10 (4.4%)	1 (0.5%)	5 (2.6%)	1 (0.5%)	13 (8.3%)	16 (10.3%)	7 (4.2%)	7 (4.2%)
Undefined etiology	13 (5.8%)	14 (6.3%)	9 (4.0%)	24 (12.6%)	20 (10.5%)	18 (9.4%)	10 (6.4%)	14 (9.0%)	8 (4.8%)	7 (4.2%)
Study Day of First Dialysis										
N	223	224	226	190	191	191	157	156	168	168
Mean	-1651	-1777	-1620	-1529	-1616	-1629	-2067	-2207	-1769	-1757
Std. Dev.	1913.9	1886.5	1592.5	1576.5	1648.9	1625.9	2225.4	2243.3	2102.0	2050.6
Median	-1018	-1199	-1088	-1006	-1211	-1019	-1254	-1319	-1071	-1018
Min-Max	-12681 - -118	-13473 - -136	-9734 - -125	-1053 - -161	-9310 - -154	-8598 - -101	-12332 - -156	-10519 - -141	-13481 - -126	-13301 - -145
Mode of Current Dialysis										
Hemodialysis	223 (100.0%)	224 (100.0%)	226 (100.0%)	176 (92.6%)	177 (92.7%)	171 (89.5%)	157 (100.0%)	155 (99.4%)	159 (94.6%)	158 (94.0%)
Peritoneal Dialysis				14 (7.4%)	14 (7.3%)	20 (10.5%)		1 (0.6%)	9 (5.4%)	10 (6.0%)
Vascular Access Type (Hemodialysis, n)										
Arteriovenous fistula	134 (60.1%)	120 (53.6%)	135 (59.7%)	154 (80.5%)	146 (76.4%)	149 (77.9%)	132 (84.1%)	117 (75.0%)	112 (66.7%)	107 (63.7%)
Arteriovenous fistula / inwelling (tunneled) catheter	1 (0.4%)	1 (0.4%)	3 (1.3%)	1 (0.5%)		1 (0.5%)			1 (0.6%)	
Arteriovenous graft	66 (29.6%)	78 (34.6%)	60 (26.5%)	12 (6.3%)	16 (8.4%)	11 (5.8%)	18 (11.5%)	26 (16.7%)	29 (17.4%)	38 (22.6%)
Arteriovenous graft / inwelling (tunneled) catheter	1 (0.4%)		1 (0.4%)						1 (0.6%)	
Inwelling (tunneled) catheter	20 (9.0%)	25 (11.1%)	27 (11.9%)	9 (4.7%)	15 (7.8%)	10 (5.2%)	7 (4.5%)	12 (7.7%)	16 (9.5%)	13 (7.7%)
Not specified / missing	1 (0.4%)									
Peritoneal Dialysis Type (n)										
APD							1 (100.0%)			
CAPD				6 (42.9%)	7 (50.0%)	7 (35.0%)			1 (11.1%)	3 (30.0%)
CCPD				7 (50.0%)	6 (42.9%)	10 (50.0%)			6 (66.7%)	7 (70.0%)
NIPD				1 (7.1%)	1 (7.1%)	3 (15.0%)				
Other									2 (22.2%)	
Study Day of First Erythropoietic Agent Administration										
N	218	226	226	190	190	191	156	153	168	164
Mean	-1252	-1460	-1305	-1239	-1147	-1256	-1359	-1378	-1191	-1285
Std. Dev.	1074.9	1332.9	1030.9	892.4	897.9	1084.4	1068.4	1158.6	936.2	1214.0
Median	-911	-1112	-992	-967	-1007	-916	-1006	-1097	-976	-863
Min-Max	-5608 - -88	-10628 - -88	-5404 - -86	-5153 - -98	-5059 - -93	-5191 - -88	-4806 - -156	-5642 - -129	-5418 - -106	-6975 - -100
Previous Epoetin Type										
Epoetin Alfa	176 (79.8%)	179 (79.5%)	179 (78.8%)	22 (11.6%)	23 (12.0%)	23 (12.0%)			113 (67.3%)	104 (61.9%)
Epoetin Beta	47 (21.1%)	46 (20.5%)	48 (21.2%)	168 (88.4%)	168 (88.0%)	168 (88.0%)			55 (32.7%)	64 (38.1%)
Carbopoetin							157 (100.0%)	156 (100.0%)		
Route of Study Drug Administration										
IV	223 (100.0%)	224 (100.0%)	226 (100.0%)				157 (100.0%)	156 (100.0%)	113 (67.3%)	114 (67.9%)
SC				190 (100.0%)	191 (100.0%)	191 (100.0%)			55 (32.7%)	54 (32.1%)

**Table 34: Baseline Dialysis Status
Phase 3 Maintenance Studies (ITT Population)**

	BA16739			BA16740			BA17283			BA17284	
	RO503821 1 ¹ / ₂ weeks (N =223)	RO503821 1 ¹ / ₄ weeks (N =224)	Reference (N =226)	RO503821 1 ¹ / ₂ weeks (N =190)	RO503821 1 ¹ / ₄ weeks (N =191)	Reference (N =191)	RO503821 1 ¹ / ₂ weeks (N =157)	Reference (N =156)	RO503821 1 ¹ / ₂ weeks (N =168)	Reference (N =168)	
Type of Dialysis											
Hemodialysis	223 (100.0%)	224 (100.0%)	226 (100.0%)	176 (92.6%)	177 (92.7%)	171 (89.5%)	157 (100.0%)	155 (99.4%)	159 (94.6%)	158 (94.0%)	
Peritoneal Dialysis				14 (7.4%)	14 (7.3%)	20 (10.5%)		1 (0.6%)	9 (5.4%)	10 (6.0%)	
Kt/V											
N	103	104	97	121	131	119	116	106	108	105	
Mean	1.58	1.62	1.60	1.53	1.57	1.54	1.57	1.57	1.61	1.62	
Std. Dev.	0.288	0.247	0.283	0.265	0.337	0.287	0.338	0.337	0.270	0.439	
Median	1.55	1.59	1.57	1.48	1.47	1.46	1.49	1.51	1.60	1.52	
Min-Max	1.20 - 3.01	1.20 - 2.55	1.20 - 2.78	1.19 - 2.62	1.07 - 2.90	1.15 - 3.13	1.18 - 3.26	1.16 - 3.32	1.20 - 2.59	1.10 - 4.03	
Kt/V Weekly											
N				13	14	20		1	9	10	
Mean				2.27	2.26	2.29		1.99	2.75	2.39	
Std. Dev.				0.280	0.607	0.536			0.766	0.453	
Median				2.31	2.19	2.11		1.99	2.58	2.24	
Min-Max				1.88 - 2.71	0.84 - 3.35	1.80 - 4.07		1.99 - 1.99	1.97 - 3.92	1.89 - 3.18	
GRR											
N	119	120	128	63	55	61	45	50	49	52	
Mean	74.3	73.7	74.6	74.7	73.8	73.2	118.1	74.1	73.9	73.4	
Std. Dev.	6.21	6.23	6.14	6.36	6.28	6.02	167.49	5.52	5.74	5.69	
Median	74.0	73.0	74.0	73.7	73.0	73.0	74.0	74.5	73.0	73.0	
Min-Max	57 - 95	63 - 95	65 - 99	67 - 98	65 - 91	53 - 91	66 - 764*	63 - 83	65 - 90	63 - 95	

Previous and Concomitant Iron Supplementation

The majority of patients received previous or previous/concomitant iron treatment at baseline; this percentage was similar among the treatment groups within the following studies: 77% to 81% in BA16739, 81% to 84% in BA16740, 83% to 85% in BA17283. In BA17284, 72% of patients in the Mircera group and 63% of patients in the reference group received previous or previous/concomitant iron at baseline. The most commonly administered iron supplements were iron sucrose (in 31% to 49% of patients in each treatment group across the hemoglobin maintenance studies) and ferrous gluconate (in 20% to 39% of patients in each treatment group across the hemoglobin maintenance studies). These data are presented in Table 35.

**Table 35: Previous and Concomitant Iron Supplementation at Baseline
Phase 3 Maintenance Studies (ITT Population)**

	BA16739			BA16740			BA17283			BA17284		
	RO0503821		Reference (N =226)	RO0503821		Reference (N =191)	RO0503821		Reference (N =156)	RO0503821		Reference (N =168)
	1 ¹ / ₂ weeks (N =223)	1 ¹ / ₄ weeks (N =224)		1 ¹ / ₂ weeks (N =190)	1 ¹ / ₄ weeks (N =191)		1 ¹ / ₂ weeks (N =157)	1 ¹ / ₄ weeks (N =168)				
No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	
ALL CLASSES												
Total Pts with at Least one Treatment	171 (76.7)	181 (80.8)	180 (79.6)	156 (82.1)	161 (84.3)	155 (81.2)	133 (84.7)	129 (82.7)	121 (72.0)	106 (63.1)		
Total Number of Treatments	186	187	189	162	165	159	141	135	132	108		
ANTI-ANEMIC AGENTS												
Total Pts with at Least one Treatment	171 (76.7)	181 (80.8)	180 (79.6)	156 (82.1)	161 (84.3)	155 (81.2)	133 (84.7)	129 (82.7)	120 (71.4)	106 (63.1)		
IRON SUCROSE	72 (32.3)	89 (39.7)	77 (34.1)	84 (44.2)	85 (44.5)	86 (45.0)	77 (49.0)	70 (44.9)	52 (31.0)	57 (33.9)		
FERROUS GLUCONATE	86 (38.6)	73 (32.6)	81 (35.8)	51 (26.8)	39 (20.4)	48 (25.1)	33 (21.0)	31 (19.9)	53 (31.5)	38 (22.6)		
FERROUS SULFATE	9 (3.6)	9 (4.0)	7 (3.1)	14 (7.4)	11 (5.8)	11 (5.8)		2 (1.3)	11 (6.5)	2 (1.2)		
IRON DEXTRAN	6 (2.7)	7 (3.1)	10 (4.4)	1 (0.5)	5 (2.6)	4 (2.1)	7 (4.5)	9 (5.8)	6 (3.6)	6 (3.6)		
IRON POLYMALTOSE				1 (0.5)		2 (1.0)	14 (8.9)	17 (10.9)				
FERRIC HYDROXIDE	1 (0.4)	2 (0.9)	4 (1.8)	3 (1.6)	12 (6.3)	2 (1.0)						
FERROUS FUMARATE	4 (1.8)	2 (0.9)	5 (2.2)	3 (1.6)	3 (1.6)	3 (1.6)	1 (0.6)		2 (1.2)	1 (0.6)		
IRON	3 (1.3)	2 (0.9)	4 (1.8)				5 (3.2)	5 (3.2)	2 (1.2)	1 (0.6)		
CALCIUM PHOSPHATE/ FERROUS FUMARATE/MULTIVITAMIN NOS				3 (1.6)	4 (2.1)	2 (1.0)						
*FERROUS GLYCINE SULFATE/POLYSACCHARIDE -IRONCOMPLEX								2 (1.3)	1 (0.6)	3 (1.8)		
FERRIC CHLORIDE				2 (1.1)	2 (1.0)	1 (0.5)				1 (0.6)		
CYANOCOBALAMIN/ FOLIC ACID/POLYSACCHARIDE-IRON COMPLEX	1 (0.4)								2 (1.2)	2 (1.2)		
FERROUS SUCCINATE	3 (1.3)	2 (0.9)										
POLYSACCHARIDE -IRON COMPLEX	2 (0.9)		1 (0.4)		1 (0.5)		1 (0.6)					
ASCORBIC ACID/ CYANOCOBALAMIN/ FERROUS FUMARATE/INTRINSIC FACTOR		1 (0.4)										
CYANOCOBALAMIN/ FERROUS SULFATE/FOLIC ACID					1 (0.5)							
FERROUS FUMARATE/ FOLIC ACID/MINERALS/SODIUM ASCORBATE/VITAMIN ECOMPLEX					1 (0.5)							
FERROUS GLYCINE SULFATE					1 (0.5)							
FERROUS SULFATE/ SODIUM ASCORBATE							1 (0.6)					
Total Number of Treatments	186	187	189	162	165	159	141	135	131	108		
FOLIC ACID & DERIVATIVES												
Total Pts with at Least one Treatment										1 (0.6)		
FOLIC ACID										1 (0.6)		
Total Number of Treatments										1		

Hemoglobin and Iron Parameters

There were no clinically relevant differences in iron parameters or hemoglobins between treatment groups within any of the phase 3 studies. The majority of patients enrolled were determined to be iron replete, and hemoglobin values reflected the disease status in the patient population. Baseline laboratory parameters are presented in Table 36.

Baseline Hemoglobin

To enter the studies, patients were required to have mean baseline hemoglobins between 10.5 and 13 g/dL. Mean hemoglobin at baseline was similar in all treatment groups of the phase 3

hemoglobin maintenance studies, 11.7 to 12.0 g/dL. Median hemoglobin at baseline was also similar, 11.6 to 12.0 g/dL, with an overall range of 10.3 g/dL to 13.2.0 g/dL.

Baseline Ferritin, TSAT, and Serum Iron Levels

Adequate iron status at study entry was defined as serum ferritin over 100 ug/L or TSAT over 20% in all phase 3 studies. Baseline median TSAT levels were within acceptable range and were comparable in all treatment groups across the studies: median values in the ITT population ranged from 27% to 31%, overall. Baseline median ferritin levels in each treatment group within each study were also within an acceptable range: median values in BA16739 were 453 - 522 ug/L, median values in BA16740 were 418 - 435 ug/L, median values in BA17283 were 368 - 382 ug/L, and median values in BA17284 were 482 - 515 ug/L. Median serum iron levels were comparable in all treatment groups, 11.6 to 12.9 µmol/L, across the studies.

**Table 36: Baseline Hemoglobin and Iron Parameters
Phase 3 Maintenance Studies (ITT Population)**

	BA16739			BA16740			BA17283			BA17284	
	RO0503821 1 ¹ /2 weeks (N =223)	RO0503821 1 ¹ /4 weeks (N =224)	Reference (N =226)	RO0503821 1 ¹ /2 weeks (N =190)	RO0503821 1 ¹ /4 weeks (N =191)	Reference (N =191)	RO0503821 1 ¹ /2 weeks (N =157)	Reference (N =156)	RO0503821 1 ¹ /2 weeks (N =168)	Reference (N =168)	
Hemoglobin [g/dL]											
N	223	224	226	190	191	191	157	156	168	168	
Mean	11.97	11.85	11.31	11.70	11.66	11.65	12.01	11.93	11.85	11.83	
Std. Dev.	0.652	0.649	0.640	0.724	0.713	0.697	0.676	0.664	0.660	0.688	
Median	11.97	11.91	11.97	11.68	11.64	11.62	12.00	12.00	11.91	11.75	
Q1-Q3	11.5 - 12.5	11.4 - 12.3	11.4 - 12.4	11.1 - 12.4	11.0 - 12.3	11.0 - 12.2	11.6 - 12.6	11.4 - 12.5	11.3 - 12.4	11.3 - 12.4	
Min-Max	10.5 - 13.0	10.4 - 13.1	10.5 - 13.1	10.4 - 13.0	10.4 - 13.0	10.5 - 13.1	10.5 - 13.1	10.5 - 13.0	10.3 - 13.2	10.4 - 13.1	
Serum Iron [µmol/L]											
N	223	223	225	190	191	191	156	156	165	162	
Mean	12.43	13.03	13.41	13.77	12.93	14.33	12.87	12.92	12.55	13.14	
Std. Dev.	4.538	5.879	5.680	4.671	4.702	7.638	5.457	4.951	4.156	4.672	
Median	11.55	11.90	12.17	12.87	11.80	12.53	12.00	11.90	11.72	12.40	
Q1-Q3	9.4 - 14.2	9.8 - 14.8	10.1 - 15.3	10.4 - 16.3	9.7 - 15.4	9.8 - 16.6	9.5 - 14.9	9.9 - 15.3	9.8 - 14.9	9.8 - 15.8	
Min-Max	4.7 - 34.7	3.6 - 51.6	3.9 - 61.8	4.8 - 34.0	5.6 - 31.0	4.9 - 80.5	4.8 - 51.0	5.0 - 31.5	0.5 - 31.7	5.2 - 34.5	
Ferritin [ug/L]											
N	223	223	225	190	191	190	156	156	163	163	
Mean	529.60	556.50	555.79	520.94	520.61	530.36	424.17	432.64	529.27	517.29	
Std. Dev.	384.903	347.673	380.796	414.712	423.760	401.583	334.787	271.191	268.892	301.333	
Median	453.00	521.50	504.50	417.75	426.50	435.00	367.75	382.25	515.00	481.50	
Q1-Q3	244 - 722	288 - 762	288 - 728	240 - 659	253 - 661	276 - 652	216 - 547	233 - 596	324 - 713	305 - 689	
Min-Max	27 - 3163	31 - 2170	31 - 2946	35 - 3502	42 - 3831	46 - 2498	12 - 2905	19 - 1251	58 - 1307	39 - 1542	
Transferrin Saturation [%]											
N	216	212	221	190	189	190	156	153	164	162	
Mean	29.11	30.59	32.27	32.44	30.48	33.26	30.94	30.03	30.04	31.11	
Std. Dev.	10.653	11.120	10.796	13.101	11.069	16.829	16.016	11.987	10.612	11.918	
Median	27.00	27.69	30.50	30.45	27.55	30.50	28.42	28.00	28.50	30.00	
Q1-Q3	22.5 - 33.0	24.0 - 35.3	25.0 - 38.5	23.0 - 39.0	22.5 - 36.5	22.8 - 40.0	22.3 - 35.3	21.5 - 33.5	22.9 - 35.0	23.0 - 35.7	
Min-Max	11.0 - 89.0	8.0 - 79.5	11.5 - 72.2	11.0 - 96.5	10.5 - 71.5	11.0 - 160.5	11.0 - 160.0	10.5 - 74.5	1.0 - 74.5	9.9 - 101.9	

Ferritin and TSAT Levels During the study

Iron was supplemented based on iron studies. In the ITT population, mean and median ferritin and TSAT parameters stayed well within acceptable ranges (defined as ferritin values above 100 and < 800µg/L; TSAT > 20% and < 50%) in each treatment group of each study throughout the study period. Overall, the patient population was considered to be iron replete. Despite variation in the individual TSAT and ferritin parameters, iron deficiency, defined as patients with TSAT levels < 20% and ferritin levels < 100 µg/L, occurred in no more than 5 patients (< 4%) per month in any treatment group during any of the hemoglobin maintenance studies. Iron deficiency is shown by month in Table 37.

Table 37: Iron Deficiency in Maintenance Studies (ITT Population)

	BA16739			BA16740			BA17283			BA17284	
	RO0503821 1 ¹ / ₂ weeks (N =223)	RO0503821 1 ¹ / ₄ weeks (N =224)	Reference (N =226)	RO0503821 1 ¹ / ₂ weeks (N =190)	RO0503821 1 ¹ / ₄ weeks (N =191)	Reference (N =191)	RO0503821 1 ¹ / ₂ weeks (N =157)	Reference (N =156)	RO0503821 1 ¹ / ₂ weeks (N =168)	Reference (N =168)	
Patients with TSAT < 20%											
Baseline	32 (14.8%)	22 (10.4%)	19 (9.6%)	23 (12.1%)	24 (12.7%)	27 (14.2%)	27 (17.3%)	26 (17.0%)	24 (14.6%)	25 (15.4%)	
Month 1	33 (17.6%)	4 (2.2%)	3 (13.0%)	41 (24.1%)	19 (7.4%)	13 (16.3%)	24 (17.0%)	32 (23.5%)	27 (18.9%)	6 (13.6%)	
Month 3	40 (20.3%)	12 (6.3%)	21 (10.2%)	40 (23.4%)	16 (9.0%)	26 (14.9%)	33 (23.4%)	34 (23.4%)	35 (23.5%)	29 (18.7%)	
Month 5	38 (20.0%)	18 (9.9%)	24 (11.6%)	34 (19.7%)	18 (10.7%)	40 (22.2%)	32 (22.9%)	24 (16.9%)	32 (21.5%)	31 (19.5%)	
Month 7	34 (18.3%)	8 (4.6%)	32 (16.2%)	45 (27.6%)	31 (18.8%)	35 (19.9%)	36 (26.7%)	35 (25.5%)	30 (20.7%)	28 (18.1%)	
Month 9	35 (19.6%)	15 (8.8%)	39 (20.1%)	32 (20.1%)	23 (14.5%)	34 (19.8%)	24 (18.9%)	24 (18.8%)	26 (20.5%)	32 (21.6%)	
Patients with FERRON < 100 ng/mL											
Baseline	15 (6.7%)	10 (4.5%)	13 (5.8%)	2 (1.1%)	3 (1.6%)	7 (3.7%)	9 (5.8%)	11 (7.1%)	6 (3.7%)	7 (4.3%)	
Month 1	19 (9.9%)	6 (3.1%)		7 (4.1%)	6 (3.4%)	1 (1.2%)	8 (5.8%)	11 (7.7%)	8 (5.4%)	2 (4.3%)	
Month 3	14 (7.0%)	5 (2.5%)	8 (3.9%)	4 (2.3%)	5 (2.8%)	5 (2.8%)	10 (7.2%)	5 (3.4%)	4 (2.7%)	2 (1.3%)	
Month 5	11 (5.6%)	6 (3.1%)	6 (2.9%)	6 (3.5%)	7 (4.1%)	7 (3.9%)	12 (8.6%)	8 (5.6%)	3 (2.0%)	2 (1.2%)	
Month 7	11 (5.7%)	4 (2.2%)	11 (5.5%)	7 (4.2%)	7 (4.2%)	5 (2.9%)	7 (5.2%)	6 (4.3%)	4 (2.8%)	7 (4.5%)	
Month 9	11 (6.0%)	3 (1.7%)	8 (4.1%)	7 (4.4%)	8 (4.9%)	4 (2.3%)	10 (7.9%)	5 (3.9%)	2 (1.5%)		
Patients with TSAT < 20% and FERRON < 100 ng/mL											
Baseline	1 (0.5%)		1 (0.5%)	2 (1.1%)			1 (0.6%)	1 (0.7%)	1 (0.6%)		
Month 1	5 (2.7%)			3 (1.8%)	1 (0.6%)		2 (1.5%)	4 (3.0%)	3 (2.1%)		
Month 3	4 (2.1%)		1 (0.5%)	4 (2.4%)	2 (1.1%)	1 (0.6%)	2 (1.5%)	3 (2.1%)	1 (0.7%)	1 (0.7%)	
Month 5	4 (2.1%)	2 (1.1%)	2 (1.0%)	2 (1.2%)	3 (1.8%)	4 (2.2%)	5 (3.6%)	1 (0.7%)	3 (2.0%)		
Month 7	5 (2.7%)	1 (0.6%)	4 (2.0%)	4 (2.5%)	2 (1.2%)	2 (1.2%)	3 (2.2%)		1 (0.7%)	1 (0.7%)	
Month 9	4 (2.3%)	1 (0.6%)	5 (2.6%)	3 (1.9%)	4 (2.6%)	1 (0.6%)	1 (0.8%)	2 (1.6%)	1 (0.8%)		

Dose Adjustments

Dose adjustments were required by almost all patients, resulting in a large proportion of patients with hemoglobins in the evaluation period that were virtually identical to those at baseline. For BA16739 and BA16740, dose increases, alone, were more common in the Mircera Q4W group than in the other two groups, whereas dose decreases, alone, were more common in both Mircera groups compared with the epoetin group (Table 38). For BA17283 and BA17284, dose decreases, alone, were more common in the Mircera group, whereas increases, alone, were more common in the darbepoetin alfa or epoetin groups, respectively.

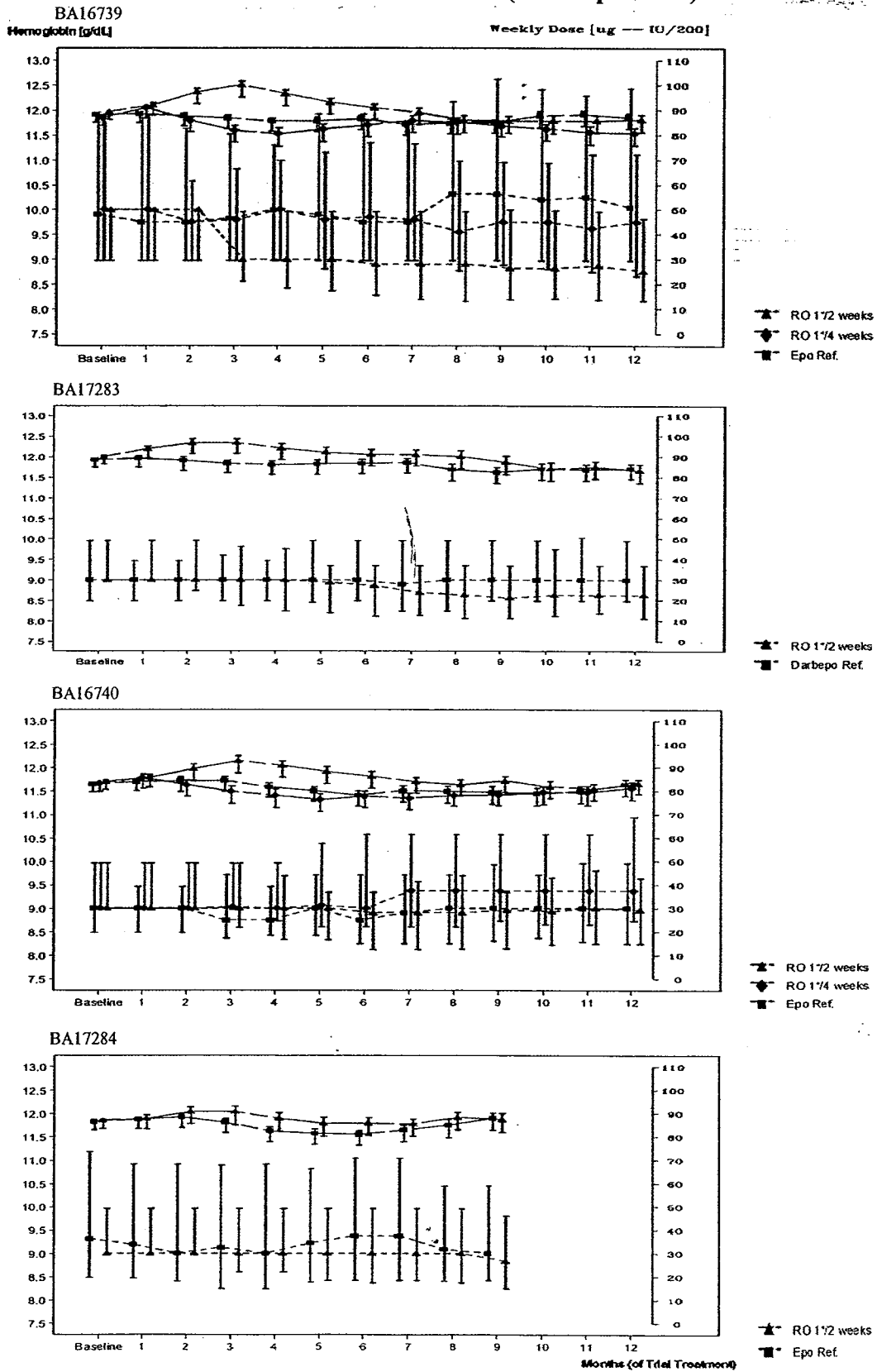
**Table 38: Dose Adjustments (Based on Weekly Dose)
Phase 3 Maintenance Studies (Safety Population)**

Study	R00503821 1*/2 weeks	R00503821 1*/4 weeks	Reference
BA16739	N= 221, n= 221	N= 220, n= 220	N= 225, n= 225
No Dose Change	10 (4.5%)	26 (11.8%)	20 (8.9%)
Any Dose Change	211 (95.5%)	194 (88.2%)	205 (91.1%)
Dose Increase(s) only	11 (5.0%)	34 (15.5%)	26 (11.6%)
Dose Decrease(s) only	28 (12.7%)	35 (15.9%)	17 (7.6%)
Dose Decrease(s) and Increase(s)	172 (77.8%)	125 (56.8%)	162 (72.0%)
BA16740	N= 190, n= 190	N= 190, n= 190	N= 191, n= 191
No Dose Change	22 (11.6%)	24 (12.6%)	30 (15.7%)
Any Dose Change	168 (88.4%)	166 (87.4%)	161 (84.3%)
Dose Increase(s) only	20 (10.5%)	44 (23.2%)	30 (15.7%)
Dose Decrease(s) only	38 (20.0%)	30 (15.8%)	27 (14.1%)
Dose Decrease(s) and Increase(s)	110 (57.9%)	92 (48.4%)	104 (54.5%)
BA17283	N= 153, n= 153		N= 156, n= 156
No Dose Change	15 (9.8%)		16 (10.3%)
Any Dose Change	138 (90.2%)		140 (89.7%)
Dose Increase(s) only	17 (11.1%)		29 (18.6%)
Dose Decrease(s) only	23 (15.0%)		15 (9.6%)
Dose Decrease(s) and Increase(s)	98 (64.1%)		96 (61.5%)
BA17284	N= 165, n= 165		N= 168, n= 168
No Dose Change	12 (7.3%)		19 (11.3%)
Any Dose Change	153 (92.7%)		149 (88.7%)
Dose Increase(s) only	11 (6.7%)		24 (14.3%)
Dose Decrease(s) only	23 (13.9%)		17 (10.1%)
Dose Decrease(s) and Increase(s)	119 (72.1%)		108 (64.3%)

Figure 11 shows the median equivalent QW dose of trial treatment and mean hemoglobin over time for all four hemoglobin maintenance studies. Conversion categories coupled with adjustment guidance resulted in hemoglobin values that were virtually identical to baseline throughout the studies.

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**Figure 11: Median Equivalent Weekly Dose and Mean Hemoglobin over Time
Phase 3 Maintenance Studies (ITT Population)**



Primary Efficacy Results

The primary objective of BA16739, BA16740, BA17283, and BA17284 was to demonstrate that Mircera administered IV or SC would maintain hemoglobins in dialysis patients on prior IV or SC erythropoiesis stimulating agents. The primary efficacy parameter was the change in hemoglobins between baseline and the evaluation period. The analysis was performed on the PP population (Table 39).

- The change in hemoglobin between baseline and the evaluation period was comparable between the Mircera treatment group(s) and the reference group within each of the four studies, and most were close to zero (no change). The largest changes from baseline occurred in the Mircera Q4W group of BA16740 (-0.21 g/dL) and the Mircera Q2W group of BA17284 (0.25g/dL). Both were within the range of expected variation over time in this patient population.
- Differences in Mircera dosing regimen had no discernible effect on changes in mean hemoglobins from baseline to the evaluation period. In studies with a Q4W Mircera treatment group (BA16739 and BA16740), changes in hemoglobins were similar to changes in both the Mircera Q2W group and the reference groups.
- In BA16739 and BA17283 Mircera was administered intravenously. In BA16740 Mircera was administered subcutaneously, and in BA16284 Mircera was administered IV or SC using PFS. Within each study, the route of administration did not affect the comparability of Mircera to the reference medications in maintaining hemoglobins. This is discussed in more detail in the analyses of subpopulations. BA16739, BA16740 and BA17284 used epoetin (alfa or beta) as the reference medication.
- Study BA17283 used darbepoetin alfa as the reference medication. In each study, median changes from baseline in mean hemoglobins were comparable between the Mircera group(s) and the reference group, indicating that Mircera adequately maintained hemoglobins in patients regardless of their previous medication: epoetin alfa, epoetin beta, or darbepoetin alfa.

**Table 39: Change in Hemoglobin
Phase 3 Maintenance Studies (PP Population)**

Study	Treatment	N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
BA16739	RO0503821 1*/2 weeks	188	-0.10	1.06	-3.14	-0.75	-0.07	0.63	2.67
	RO0503821 1*/4 weeks	172	0.01	0.96	-3.49	-0.60	0.02	0.61	2.34
	Reference	180	-0.10	0.92	-2.64	-0.75	0.00	0.52	2.14
BA16740	RO0503821 1*/2 weeks	154	-0.00	0.96	-3.16	-0.57	0.06	0.64	2.53
	RO0503821 1*/4 weeks	153	-0.11	0.97	-3.43	-0.68	-0.21	0.47	2.89
	Reference	167	-0.12	1.04	-4.45	-0.67	0.01	0.53	2.90
BA17283	RO0503821 1*/2 weeks	123	0.05	0.96	-2.69	-0.53	0.10	0.74	2.57
	Reference	126	-0.10	0.92	-2.88	-0.75	-0.08	0.65	1.87
BA17284	RO0503821 1*/2 weeks	123	0.14	0.93	-1.96	-0.66	0.25	0.86	2.19
	Reference	133	-0.01	1.03	-2.89	-0.70	-0.05	0.60	4.21

Additional analyses performed with the ITT and eligible populations supported the primary analysis performed with the PP population. In the ITT population median changes from baseline in mean hemoglobins were similar between treatment groups within each study. In the eligible population, median changes from baseline in mean hemoglobins were similar between treatment groups within each study.

Non-inferiority testing was performed on the change from baseline in mean hemoglobin, comparing the Mircera groups to the reference groups. This was based on an ANCOVA with a non-inferiority limit of -0.75g/dL. A 95% confidence level was used for BA17283 and BA17284. A 97.5% confidence level was chosen for BA16739 and BA16740 in order to adjust for the multiplicity resulting from the independent comparisons of two Mircera groups with one reference group. In all studies and in all analysis populations the lower limits of the CI were greater than -0.75 (values ranged from -0.371 to 0.021), confirming the non-inferiority of Mircera to epoetin alfa, epoetin beta and darbepoetin alfa. All p-values were statistically significant ($p < 0.0001$). Non-inferiority tests for treatment differences in hemoglobin change from baseline are presented for the PP population in **Table 40**. Results for the ITT population and eligible population supported those in the PP population.

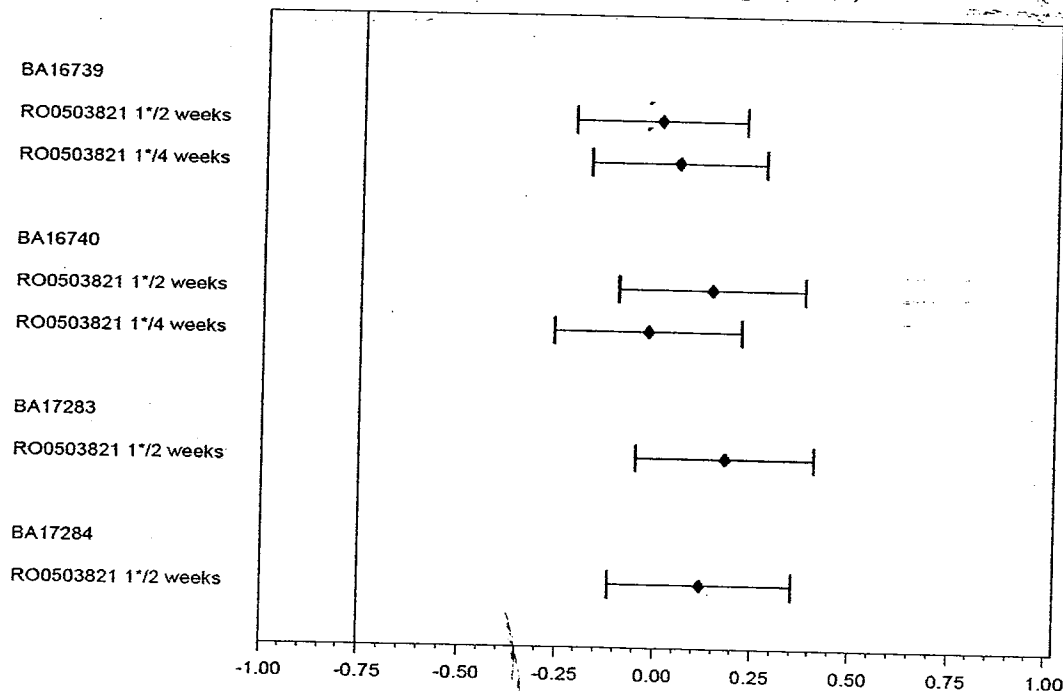
Non-inferiority was confirmed irrespective of dosing regimen (Q2W or Q4W [BA16739 and BA16740]) or route of administration (IV [BA16739 and BA17283], SC [BA16740], and IV or SC [BA17284]), or presentation (prefilled syringes [BA17284] or vials [all other studies]). The CI of the non-inferiority test are presented graphically for the PP population in **Figure 12**.

**Table 40: Non-Inferiority Test for Treatment Differences (-0.75 g/dL Limit)
Hemoglobin Change in Phase 3 Maintenance Studies (PP Population)**

Study	Treatment	R00503821 Adj. Mean Change	Reference Adj. Mean Change	Difference		DF	P-Value of NI Test	Lower CI*	Upper CI*
				Between Groups	Standard Error				
BA16739	R00503821 1*/2 weeks (N = 188)	-0.071 (n=188)	-0.075 (n=180)	0.004	0.0973	534	<.0001	-0.215	0.223
	R00503821 1*/4 weeks (N = 172)	-0.025 (n=172)	-0.075 (n=180)	0.051	0.0997	534	<.0001	-0.173	0.275
BA16740	R00503821 1*/2 weeks (N = 154)	0.032 (n=154)	-0.109 (n=167)	0.141	0.1063	469	<.0001	-0.098	0.380
	R00503821 1*/4 weeks (N = 153)	-0.131 (n=153)	-0.109 (n=167)	-0.022	0.1065	469	<.0001	-0.262	0.217
BA17283	R00503821 1*/2 weeks (N = 123)	0.063 (n=123)	-0.116 (n=126)	0.180	0.1162	246	<.0001	-0.049	0.408
BA17284	R00503821 1*/2 weeks (N = 123)	0.088 (n=123)	-0.030 (n=133)	0.118	0.1190	251	<.0001	-0.116	0.353

* For BA16739 and BA16740, 97.5% CI; for BA17283 and BA17284, 95% CI; DF = degrees of freedom

**Figure 12: CI for Difference in Primary Endpoint (Mircera vs Reference)
Phase 3 Maintenance Studies (PP Population)**



Secondary Efficacy Results

The secondary efficacy endpoints for the phase 3 hemoglobin maintenance studies were the number of patients maintaining average hemoglobins during the evaluation period within ± 1 g/dL of their average baseline hemoglobin, and the incidence of RBC transfusions during the dose titration and evaluation periods.

Number of Patients Maintaining Hemoglobin

The majority of patients in each of the treatment groups (Mircera or reference) maintained average hemoglobins during the evaluation period within ± 1 g/dL of their average baseline hemoglobins (66% to 76%). A summary of patients maintaining average hemoglobin during the evaluation period within ± 1 g/dL of their average baseline hemoglobin is provided for the ITT population in **Table 41**.

In the ITT population, the percentages of patients who maintained hemoglobins within this range were generally similar between the Mircera treatment group(s) and the epoetin or darbepoetin alfa reference groups in each study. The largest between-treatment differences were seen in BA16740 and BA17283. The percentages of patients who maintained average hemoglobin within ± 1 g/dL of their average baseline hemoglobins in each treatment group of BA17284 and BA16739 ranged from 67% to 69%. The different Mircera treatment regimens (Q2W or Q4W) were comparable to each other and to the reference group in BA16739. In BA16740, the Q4W group was not comparable to the reference group. The percentages of patients with hemoglobin increases > 1 g/dL were similar among treatment groups within each study, with the exception of BA17283, in which 20% of patients in the Mircera group compared with 8% in the reference group had hemoglobin increases greater than 1 g/dL. In all studies, the proportions of patients with hemoglobin decreases over 1 g/dL were similar between the Mircera and reference groups. In general, results in the PP population were similar to those in the ITT population.

**Table 41: Patients Maintaining Hemoglobin Within 1 g/dL of Baseline
Phase 3 Maintenance Studies (ITT Population)**

Study		R00503821 1*/2 weeks	R00503821 1*/4 weeks	Reference
BA16739		N = 223, n= 196	N = 224, n= 188	N = 226, n= 205
	n of Patients Maintaining Stable Hemoglobin			
	Above	24 (12.2%)	30 (16.0%)	24 (11.7%)
	Maintained	133 (67.9%)	127 (67.6%)	138 (67.3%)
	Below	39 (19.9%)	31 (16.5%)	43 (21.0%)
BA16740		N = 190, n= 164	N = 191, n= 168	N = 191, n= 176
	n of Patients Maintaining Stable Hemoglobin			
	Above	16 (9.8%)	20 (11.9%)	18 (10.2%)
	Maintained	124 (75.6%)	111 (66.1%)	127 (72.2%)
	Below	24 (14.6%)	37 (22.0%)	31 (17.6%)
BA17283		N = 157, n= 139		N = 156, n= 142
	n of Patients Maintaining Stable Hemoglobin			
	Above	28 (20.1%)		11 (7.7%)
	Maintained	91 (65.5%)		102 (71.8%)
	Below	20 (14.4%)		29 (20.4%)
BA17284		N = 168, n= 143		N = 168, n= 158
	n of Patients Maintaining Stable Hemoglobin			
	Above	24 (16.8%)		23 (14.6%)
	Maintained	98 (68.5%)		107 (67.7%)
	Below	21 (14.7%)		28 (17.7%)

RBC Transfusions

The percentage of patients requiring blood transfusions during the titration and evaluation periods was similar between treatment groups within each of the hemoglobin maintenance studies. Overall, 6% to 12% of patients in the Mircera groups required transfusions compared with 8% to 11% in the reference groups. A similar percentage of patients in the Q4W Mircera treatment groups compared with patients in the Q2W Mircera groups or the reference groups had blood transfusions: 7% compared with 10% and 8%, respectively, in BA16739; and 11% compared with 6% and 10%, respectively, in BA16740. The incidence of blood transfusions due to AE during the titration and evaluation periods was similar between treatment groups within the hemoglobin maintenance studies, between 6% and 13% in each treatment group. Blood transfusion results in the ITT population and in the eligible population were similar to those in the safety population. Fewer patients required blood transfusion in the PP population, in which patients with RBC transfusions or blood loss within weeks 21 to 33 were excluded from analyses, unless the blood transfusion was due to lack of effect. A summary of blood transfusions for the phase 3 hemoglobin maintenance studies is presented in **Table 42**.

Table 42: Blood Transfusion in Phase 3 Maintenance Studies (Safety Population)

Study	Treatment	All Blood Transfusion			Units Transfused		Blood Transfusions for AEs					
		Total Pts with at Least one BT		Mean BFs per patient	Mean Units per BT	Median Units per BT	Total Pts with at Least one BT		Total Number of BFs			
		N	(%)				N	(%)	N	(%)		
BA16739	RO0503821 1*/2 weeks (N = 221)	21	(9.5%)	51	(38.1%)	2.43	1.63	2.00	18	(8.1%)	45	(36.3%)
	RO0503821 1*/4 weeks (N = 220)	16	(7.3%)	42	(31.3%)	2.63	1.57	1.00	16	(7.3%)	42	(33.9%)
	Reference (N = 225)	17	(7.6%)	41	(30.6%)	2.41	1.88	2.00	16	(7.1%)	37	(29.8%)
BA16740	RO0503821 1*/2 weeks (N = 190)	12	(6.3%)	34	(27.0%)	2.83	1.53	1.00	12	(6.3%)	34	(27.0%)
	RO0503821 1*/4 weeks (N = 190)	20	(10.5%)	44	(34.9%)	2.20	1.82	2.00	20	(10.5%)	44	(34.9%)
	Reference (N = 191)	19	(9.9%)	48	(38.1%)	2.53	1.67	2.00	19	(9.9%)	48	(38.1%)
BA17283	RO0503821 1*/2 weeks (N = 153)	19	(12.4%)	41	(51.9%)	2.16	1.46	1.00	19	(12.4%)	36	(50.7%)
	Reference (N = 156)	16	(10.3%)	38	(48.1%)	2.38	1.39	1.00	16	(10.3%)	35	(49.3%)
BA17284	RO0503821 1*/2 weeks (N = 165)	16	(9.7%)	37	(39.4%)	2.31	1.65	1.00	16	(9.7%)	37	(39.4%)
	Reference (N = 168)	19	(11.3%)	57	(60.6%)	3.00	1.79	2.00	19	(11.3%)	57	(60.6%)

Hemoglobin over Time

In general, the median change from baseline in hemoglobin over time was close to zero in all groups in all studies. However, a transient increase in hemoglobin values occurred during the titration period, at approximately months two through four, in the Mircera Q2W treatment groups of each study. During this period the median change in hemoglobin (in the Mircera Q2W treatment groups) did not exceed 0.77 g/dL in any study population.

Figure 13 shows the median change from baseline in hemoglobin over time for the ITT population. Throughout the study period, the mean and median monthly hemoglobins in each of the treatment groups in each of the hemoglobin maintenance studies remained within the clinically acceptable range for the treatment of dialysis patients, 11 to 13 g/dL.

Mean hemoglobins at each study period (baseline, titration, and evaluation) reflected what was seen in the monthly change from baseline over time. Overall, treatment groups within each study were comparable, and all treatment period means and medians were within the acceptable treatment range, 11 to 13 g/dL. In addition, a slight increase in mean hemoglobins was seen in the Q2W treatment regimen during the titration period. However, this increase was transient. Average hemoglobins are shown by treatment period for the ITT population in **Table 43**.

**Figure 13: Median Hemoglobin Change
Phase 3 Maintenance Studies (ITT Population)**

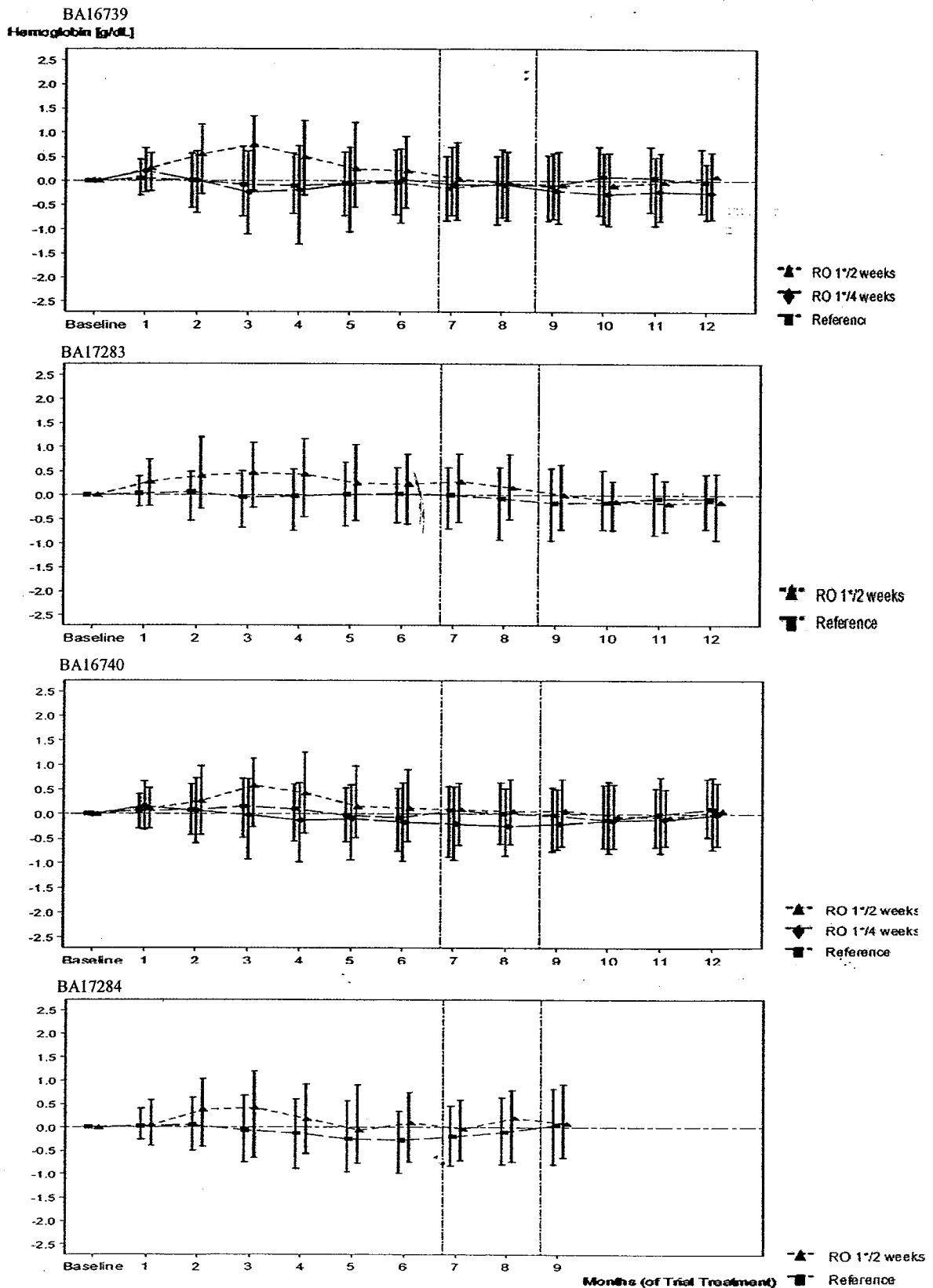


**Table 43: Mean Hemoglobin by Study Period
Phase 3 Maintenance Studies (ITT Population)**

Treatment	Study	N	Mean	Std	Minimum	Q1	Median	Q3	Maximum
Baseline (Days -30- +1)									
R00503821 1*/2 weeks	BA16739	223	11.97	0.65	10.50	11.51	11.97	12.51	13.04
	BA16740	190	11.70	0.72	10.36	11.09	11.68	12.38	13.00
	BA17283	157	12.01	0.68	10.47	11.55	12.00	12.58	13.10
	BA17284	168	11.85	0.66	10.25	11.35	11.91	12.39	13.21
R00503821 1*/4 weeks	BA16739	224	11.85	0.65	10.36	11.40	11.91	12.33	13.13
	BA16740	191	11.66	0.71	10.39	11.04	11.64	12.26	13.01
Reference	BA16739	226	11.91	0.64	10.50	11.41	11.97	12.43	13.05
	BA16740	191	11.65	0.70	10.46	11.02	11.62	12.17	13.07
	BA17283	156	11.93	0.66	10.53	11.44	12.00	12.51	13.03
	BA17284	168	11.83	0.69	10.41	11.28	11.75	12.35	13.08
Titration (Days 2-201)									
R00503821 1*/2 weeks	BA16739	222	12.21	0.79	9.20	11.77	12.25	12.79	13.83
	BA16740	190	11.94	0.94	9.38	11.34	12.07	12.60	13.90
	BA17283	153	12.18	0.81	9.54	11.71	12.23	12.78	13.87
	BA17284	166	11.87	0.89	9.00	11.49	12.01	12.46	13.63
R00503821 1*/4 weeks	BA16739	220	11.72	0.95	9.02	11.07	11.73	12.40	13.94
	BA16740	190	11.53	1.02	8.66	10.79	11.62	12.33	13.69
Reference	BA16739	225	11.83	0.69	9.13	11.46	11.87	12.28	13.33
	BA16740	189	11.61	0.81	9.06	11.15	11.65	12.14	13.33
	BA17283	155	11.85	0.78	9.75	11.36	11.89	12.38	13.59
	BA17284	168	11.71	0.76	9.90	11.21	11.67	12.14	14.46
Evaluation (Days 202-258)									
R00503821 1*/2 weeks	BA16739	196	11.83	1.14	8.86	11.12	11.90	12.59	14.06
	BA16740	164	11.65	1.07	8.31	11.09	11.69	12.52	13.90
	BA17283	139	12.01	1.19	8.32	11.24	12.06	12.79	14.80
	BA17284	143	11.89	1.07	9.28	11.12	11.86	12.58	14.51
R00503821 1*/4 weeks	BA16739	188	11.76	1.11	7.93	11.18	11.86	12.46	14.33
	BA16740	168	11.39	1.06	8.09	10.70	11.44	12.20	14.17
Reference	BA16739	205	11.74	0.99	6.30	11.16	11.84	12.44	14.06
	BA16740	176	11.49	1.17	6.90	10.82	11.59	12.29	14.08
	BA17283	142	11.69	1.16	8.21	10.97	11.83	12.42	14.39
	BA17284	158	11.74	1.20	6.60	11.07	11.82	12.58	14.91
Follow-Up (Days 259-376)									
R00503821 1*/2 weeks	BA16739	187	11.79	1.01	8.89	11.14	11.93	12.51	13.80
	BA16740	161	11.60	0.96	8.57	10.96	11.44	12.31	14.80
	BA17283	129	11.67	1.16	8.02	10.98	11.84	12.57	13.61
R00503821 1*/4 weeks	BA16739	181	11.58	1.03	8.52	10.94	11.69	12.34	13.64
	BA16740	160	11.47	1.11	7.70	10.78	11.39	12.21	14.96
Reference	BA16739	196	11.84	0.96	8.69	11.24	11.90	12.49	13.89
	BA16740	172	11.52	1.11	6.74	10.91	11.53	12.19	14.58
	BA17283	134	11.70	0.99	8.13	11.15	11.86	12.37	13.64

Hemoglobin Excursions

Table 44 summarizes the proportion of patients with maximum hemoglobin values over 13.0 and 14.0 g/dL.

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Table 44: Patients with Maximum Hemoglobin > 14 (Phase 3 Maintenance, ITT)

		R00503821 1 ⁺ /2 weeks (N = 223)	R00503821 1 ⁺ /4 weeks (N = 224)	Reference (N = 226)
		N (%)	N (%)	N (%)
BA16739				
Titration Period	Number of Patients with valid Hb Value(s)	223 (100.0%)	220 (100.0%)	225 (100.0%)
	Number of Patients with Hb Value > 13 g/dL and ≤ 14 g/dL	70 (31.4%)	83 (37.7%)	90 (40.0%)
	Number of Patients with Hb Value > 14 g/dL	107 (48.0%)	47 (21.4%)	44 (19.6%)
Evaluation Period	Number of Patients with valid Hb Value(s)	196 (100.0%)	188 (100.0%)	205 (100.0%)
	Number of Patients with Hb Value > 13 g/dL and ≤ 14 g/dL	53 (27.0%)	41 (21.8%)	45 (22.0%)
	Number of Patients with Hb Value > 14 g/dL	21 (10.7%)	19 (10.1%)	12 (5.9%)
Safety Follow-Up Period	Number of Patients with valid Hb Value(s)	187 (100.0%)	181 (100.0%)	196 (100.0%)
	Number of Patients with Hb Value > 13 g/dL and ≤ 14 g/dL	52 (27.8%)	47 (26.0%)	52 (26.5%)
	Number of Patients with Hb Value > 14 g/dL	32 (17.1%)	16 (8.8%)	25 (12.8%)
BA16740				
Titration Period	Number of Patients with valid Hb Value(s)	190 (100.0%)	190 (100.0%)	189 (100.0%)
	Number of Patients with Hb Value > 13 g/dL and ≤ 14 g/dL	58 (30.5%)	57 (30.0%)	56 (29.6%)
	Number of Patients with Hb Value > 14 g/dL	59 (31.1%)	33 (17.4%)	29 (15.3%)
Evaluation Period	Number of Patients with valid Hb Value(s)	164 (100.0%)	168 (100.0%)	176 (100.0%)
	Number of Patients with Hb Value > 13 g/dL and ≤ 14 g/dL	32 (19.5%)	26 (15.5%)	38 (21.6%)
	Number of Patients with Hb Value > 14 g/dL	12 (7.3%)	7 (4.2%)	13 (7.4%)
Safety Follow-Up Period	Number of Patients with valid Hb Value(s)	161 (100.0%)	160 (100.0%)	172 (100.0%)
	Number of Patients with Hb Value > 13 g/dL and ≤ 14 g/dL	37 (23.0%)	35 (21.9%)	25 (14.5%)
	Number of Patients with Hb Value > 14 g/dL	15 (9.3%)	17 (10.6%)	18 (10.5%)
BA17283				
Titration Period	Number of Patients with valid Hb Value(s)	153 (100.0%)		155 (100.0%)
	Number of Patients with Hb Value > 13 g/dL and ≤ 14 g/dL	46 (30.1%)		56 (36.1%)
	Number of Patients with Hb Value > 14 g/dL	65 (42.5%)		28 (18.1%)
Evaluation Period	Number of Patients with valid Hb Value(s)	139 (100.0%)		142 (100.0%)
	Number of Patients with Hb Value > 13 g/dL and ≤ 14 g/dL	37 (26.6%)		27 (19.0%)
	Number of Patients with Hb Value > 14 g/dL	22 (15.8%)		9 (6.3%)
Safety Follow-Up Period	Number of Patients with valid Hb Value(s)	129 (100.0%)		134 (100.0%)
	Number of Patients with Hb Value > 13 g/dL and ≤ 14 g/dL	38 (29.5%)		33 (24.6%)
	Number of Patients with Hb Value > 14 g/dL	16 (12.4%)		10 (7.5%)
BA17284				
Titration Period	Number of Patients with valid Hb Value(s)	167 (100.0%)		168 (100.0%)
	Number of Patients with Hb Value > 13 g/dL and ≤ 14 g/dL	57 (34.1%)		60 (35.7%)
	Number of Patients with Hb Value > 14 g/dL	57 (34.1%)		27 (16.1%)
Evaluation Period	Number of Patients with valid Hb Value(s)	143 (100.0%)		158 (100.0%)
	Number of Patients with Hb Value > 13 g/dL and ≤ 14 g/dL	39 (27.3%)		39 (24.7%)
	Number of Patients with Hb Value > 14 g/dL	20 (14.0%)		12 (7.6%)

Table 45 summarizes the change in hemoglobin over time by starting dose categories. The starting dose of Mircera was based on the previous QW dose of epoetin using the following conversion categories:

Previous Weekly Epoetin Dose (Units/wk)	RO0503821 (1x/2 weeks)	RO0503821 (1x/4 weeks)
< 8,000	60 µg	120 µg
8,000 – 16,000	100 µg	200 µg
> 16,000	180 µg	360 µg

These analyses demonstrate that both the Q2W and Q4W regimens provide adequate conversion (with dose adjustments) for patients previously treated with epoetin to maintain hemoglobins. The Q2W regimen showed no additional benefit when compared to the Q4W regimen.

Table 45: Hemoglobin Change over Time by Starting Dose Category Phase 3 Maintenance Studies (ITT Population)

Treatment Group	Start Dose Category	Hb Selected Weeks [g/dL]												Average Dose per Week Evaluation Period		Change from Baseline			
		WK3	WK6	WK9	WK12	WK15	WK18	WK21	WK24	WK27	WK30	WK33	WK36	n	Mean	Median	Mean	Median	
RO0503821 1*/2																			
	<8000	0.21	0.35	0.54	0.65	0.58	0.37	0.35	0.27	0.19	0.10	0.06	0.01	348	24	20	-7	-10	
	8000-16000	0.26	0.33	0.53	0.25	0.12	0.08	-0.07	-0.02	-0.04	-0.03	-0.10	-0.11	190	44	38	-7	-13	
	>16000	0.17	0.16	0.19	0.14	0.28	0.02	0.13	0.09	0.07	-0.16	0.16	-0.27	81	74	62	-11	-27	
	Total	0.21	0.33	0.48	0.50	0.40	0.28	0.22	0.14	0.11	0.04	0.04	-0.05	619	37	28	-8	-13	
RO0503821 1*/4																			
	<8000	0.23	0.30	0.08	0.02	0.19	0.24	0.08	-0.10	0.09	0.20	-0.13	-0.34	184	34	30	3	0	
	8000-16000	0.29	0.19	-0.36	-0.51	-0.31	-0.28	-0.50	-0.55	0.03	0.10	-0.02	-0.29	104	65	50	17	0	
	>16000	0.27	0.02	-0.69	-0.88	-0.68	-0.63	-0.64	-0.75	-0.39	-0.35	-0.41	-0.48	60	124	93	37	8	
	Total	0.24	0.21	-0.19	-0.24	-0.07	0.02	-0.17	-0.31	0.00	0.08	-0.12	-0.34	348	59	38	13	0	
Combined Reference*																			
	<8000	-0.07	-0.12	-0.17	-0.15	-0.10	-0.08	-0.14	-0.17	-0.10	-0.07	-0.12	-0.12	358	4651	3703	1146	0	
	8000-16000	0.08	0.11	0.07	0.17	-0.09	-0.05	0.01	-0.04	-0.03	-0.18	-0.12	-0.07	209	9657	8938	571	0	
	>16000	0.26	0.20	0.20	0.15	0.14	-0.08	0.15	0.10	0.10	0.00	-0.05	-0.02	99	21583	18000	-3306	-2063	
	Total	0.03	0.00	-0.07	0.01	-0.07	-0.07	-0.07	-0.07	-0.05	-0.10	-0.10	-0.10	666	8739	5925	304	0	
Epoetin Reference																			
	<8000	-0.09	-0.13	-0.23	-0.15	-0.10	-0.12	-0.22	-0.21	-0.11	-0.09	-0.08	-0.12	275	6122	4997	1474	0	
	8000-16000	0.08	0.19	0.10	0.21	-0.10	-0.07	-0.03	-0.05	-0.10	-0.19	-0.12	0.00	169	12022	10000	674	-0	
	>16000	0.31	0.20	0.22	0.28	0.16	-0.07	0.22	0.15	0.10	0.00	-0.06	-0.01	89	23996	20000	-3676	-3450	
	Total	0.04	0.00	-0.05	0.05	-0.08	-0.10	-0.09	-0.10	-0.07	-0.10	-0.10	-0.04	533	10977	7500	360	0	

Dosing Conclusions for the Phase 3 Maintenance Studies

At the end of the 8-week evaluation period, the primary efficacy analysis using the ANCOVA model showed that treatment with Mircera Q2W and Mircera Q4W, as specified by the protocol, was non-inferior to treatment with epoetin alfa and beta (BA16739, BA16740 and BA17284) and darbepoetin alfa (BA17283). Median changes from baseline in mean hemoglobin (ITT population) were close to zero (no change) in the Mircera treatment group(s) and the reference group of each study during the evaluation period. The majority (66% to 76%) of patients in each of the treatment groups (Mircera or reference) maintained average hemoglobins during the

- The primary efficacy parameter, the hemoglobin response rate, defined as an increase in hemoglobin of at least 1.0 g/dL from baseline and a hemoglobin of at least 11.0 g/dL without RBC transfusions during the anemia correction period in BA16736, and during the anemia correction and evaluation periods in BA16738 was high, 93% to 98% ($p < 0.0001$), in both cases and comparable to the reference groups. In BA16738 the adjusted mean change from baseline in hemoglobin in the Mircera was non-inferior to the darbepoetin reference group.
- The secondary efficacy parameter, the incidence of RBC transfusions during the first 24 weeks (BA16736) or the first 28 weeks (BA16738) was comparable between the Mircera treatment groups and the reference groups.
- The secondary efficacy endpoint, time to target hemoglobin response, was longer in the Mircera treatment groups compared with the reference groups in both studies.

Results from all four hemoglobin maintenance studies show that Mircera was efficacious in maintaining hemoglobins in dialysis patients currently treated with an erythropoietin:

- The primary efficacy parameter, analysis of the change in hemoglobin between the baseline and the 8-week evaluation period using the ANCOVA model, showed that Mircera Q2W and Q4W were non-inferior to treatment with epoetin alfa and beta, and Mircera Q2W was non-inferior to treatment with darbepoetin alfa ($p < 0.0001$, in all cases).
- The secondary efficacy endpoints, the number of patients maintaining average hemoglobins during the evaluation period ± 1 g/dL of their average baseline concentration and the incidence of RBC transfusions during the dose titration and evaluation periods were comparable between the Mircera treatment groups and the reference groups in all cases.

Findings were consistent and reproducible regardless of route and frequency of administration, populations studied, or presentation.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In the four phase 2 and six phase 3 studies, a total of 2737 patients received at least one dose of the study medication: 1789 received Mircera and 948 received the reference agent. This group of 2737 patients was defined as the safety population.

Safety Population

In each treatment group (Mircera vs reference), approximately three-fourths of the patients participated in a hemoglobin maintenance study and 82% were on hemodialysis (3.5% on peritoneal dialysis, 14% not on dialysis). The IV route was used in slightly over one-half of the patients (54% IV, 46% SC). **Table 46** compares the two treatment groups by clinical setting (dialysis, previous therapy, location) and by treatment regimen (injection route and frequency).

Table 46: Safety Population

	R00503821 (N = 1789)	Reference (N = 948)
Study Design		
Correction	422 (23.6%)	208 (21.9%)
Maintenance	1367 (76.4%)	740 (78.1%)
Route of Study Drug Administration		
IV	930 (52.0%)	541 (57.1%)
SC	859 (48.0%)	407 (42.9%)
Mode of Current Dialysis		
Hemodialysis	1499 (83.8%)	755 (79.6%)
Peritoneal Dialysis	64 (3.6%)	31 (3.3%)
Not yet on Dialysis	226 (12.6%)	162 (17.1%)
Schedule of Study Drug Administration		
<=1*/ week	136 (7.6%)	923 (97.4%)
1*/2 weeks	1112 (62.2%)	25 (2.6%)
1*/3 weeks	88 (4.9%)	
1*/4 weeks	453 (25.3%)	
Geographical Region		
US	641 (35.8%)	328 (34.6%)
Non-US	1148 (64.2%)	620 (65.4%)

7.1.1 Deaths

Safety Population

In the safety population, the crude mortality rate appears not to be appreciably different between the two groups (7.0% Mircera, 6.1% reference), as does the adjusted mortality rate per 100 patient exposure years (PEY) (8.2% for Mircera, 7.5% reference).

The most common cause of death was cardiac arrest (0.8% in each group). The next four most common causes of death were myocardial infarction, cardiopulmonary arrest, CRF, and sepsis. These rates appear not to be appreciably different from that expected for patients with CRF followed for the duration of the study. The apparent causes of death were typical for the CRF. **Table 47**, **Table 48**, and **Figure 14** summarize causes of death and death rate over time.

Table 47: Mortality Indices (Safety Population)

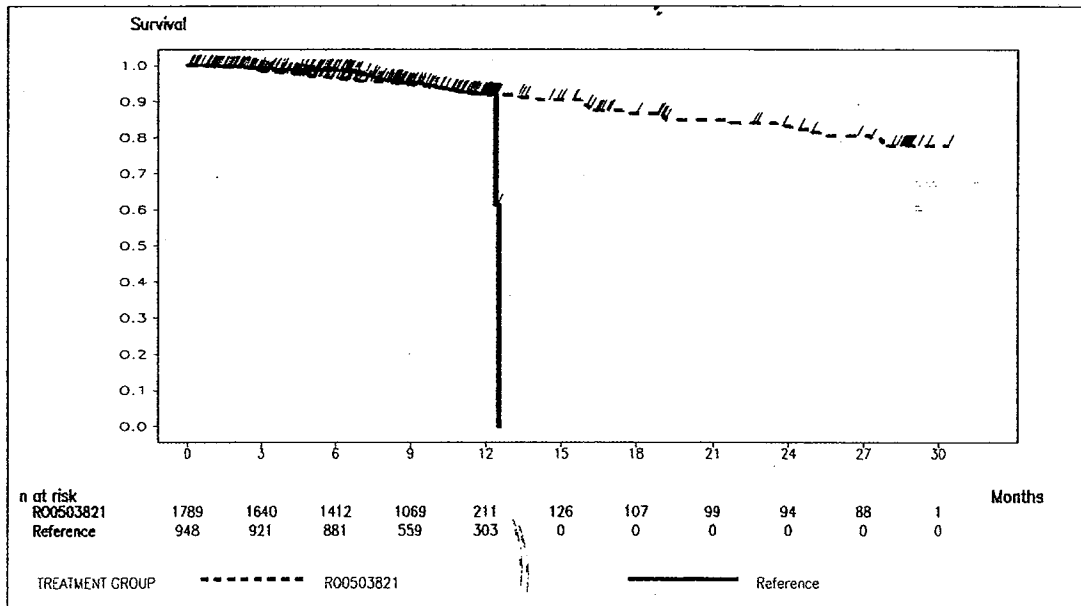
	Patients	Deaths	CMR	PEY	AMR
Mircera	1789	126	7.0	1532	8.2
Reference	948	58	6.1	778	7.5

CMR = crude mortality rate (deaths per 100 patients); PEY = patient exposure years; AMR = adjusted mortality rate (deaths per 100 PEY)

Table 48: Summary of Deaths (Safety Population)

	Mircera n = 1789 no (%)	Reference N = 948 no (%)
Total No. of Deaths	102 (6)	58 (6)
CARDIAC ARREST	15 (<1)	8 (<1)
MYOCARDIAL INFARCTION	8 (<1)	5 (<1)
CARDIO-RESPIRATORY ARREST	8 (<1)	4 (<1)
RENAL FAILURE CHRONIC	6 (<1)	5 (<1)
SEPSIS	4 (<1)	3 (<1)
SUDDEN DEATH	7 (<1)	-
CEREBROVASCULAR ACCIDENT	3 (<1)	2 (<1)
RESPIRATORY FAILURE	2 (<1)	3 (<1)
SEPTIC SHOCK	5 (<1)	-
ARRHYTHMIA	1 (<1)	3 (<1)
MULTI-ORGAN FAILURE	1 (<1)	3 (<1)
VENTRICULAR FIBRILLATION	3 (<1)	1 (<1)
CEREBRAL HAEMORRHAGE	3 (<1)	-
ISCHAEMIC STROKE	2 (<1)	1 (<1)
PNEUMONIA	2 (<1)	1 (<1)
ACUTE MYOCARDIAL INFARCTION	1 (<1)	1 (<1)
CACHEXIA	-	2 (<1)
INTESTINAL INFARCTION	2 (<1)	-
PNEUMONIA ASPIRATION	1 (<1)	1 (<1)
RENAL FAILURE	2 (<1)	-
ACUTE PULMONARY OEDEMA	1 (<1)	-
ATHEROSCLEROSIS	1 (<1)	-
BRAIN STEM HAEMORRHAGE	-	1 (<1)
BRONCHOPNEUMONIA	1 (<1)	-
CALCIPHYLAXIS	1 (<1)	-
CARDIAC FAILURE	1 (<1)	-
CARDIAC FAILURE ACUTE	-	1 (<1)
CARDIAC FAILURE CONGESTIVE	-	1 (<1)
CARDIOGENIC SHOCK	1 (<1)	-
CARDIOPULMONARY FAILURE	1 (<1)	-
CHEST INJURY	1 (<1)	-
CONGESTIVE CARDIOMYOPATHY	1 (<1)	-
CORONARY ARTERY INSUFFICIENCY	-	1 (<1)
CORONARY ARTERY THROMBOSIS	1 (<1)	-
ENTEROCOCCAL SEPSIS	-	1 (<1)
GASTROINTESTINAL HAEMORRHAGE	1 (<1)	-
HAEMORRHAGE INTRACRANIAL	1 (<1)	-
HAEMORRHAGIC STROKE	1 (<1)	-
HEPATIC CIRRHOSIS	1 (<1)	-
HYPOXIC ENCEPHALOPATHY	-	1 (<1)
INFECTION	-	1 (<1)
INTESTINAL ISCHAEMIA	-	1 (<1)
KLEBSIELLA SEPSIS	-	1 (<1)
LUNG ADENOCARCINOMA	1 (<1)	-
LUNG NEOPLASM MALIGNANT	1 (<1)	-
MENINGITIS VIRAL	1 (<1)	-
MYOCARDIAL ISCHAEMIA	-	1 (<1)
POLYTRAUMATISM	1 (<1)	-
PROSTATE CANCER	1 (<1)	-
PULMONARY EMBOLISM	1 (<1)	-
RADIATION INJURY	-	1 (<1)
RIGHT VENTRICULAR FAILURE	1 (<1)	-
STAPHYLOCOCCAL SEPSIS	1 (<1)	-
SUBARACHNOID HAEMORRHAGE	-	1 (<1)
SUBARACHNOID HAEMORRHAGE NOS	1 (<1)	-
SUBDURAL HAEMORRHAGE	-	1 (<1)
SUDDEN CARDIAC DEATH	1 (<1)	-
THROMBOTIC STROKE	1 (<1)	-
THROMBOTIC THROMBOCYTOPENIC PURPURA	-	1 (<1)
VENTRICULAR ARRHYTHMIA	-	1 (<1)
VENTRICULAR TACHYCARDIA	1 (<1)	-

Figure 14: Kaplan-Meier Plot for Deaths (Safety Population)



A Kaplan-Meier plot showed a constant death rate over time; no significant difference was seen between the two groups ($p = 0.8144$, log-rank test).

Effect of Baseline Disease

The effect of baseline disease characteristics on the incidence of death was explored using the Cox regression model. The model included the following baseline disease factors as independent variables: diabetes, ischemic heart disease (IHD), peripheral vascular disease, arterial hypertension, cerebral vascular disease, congestive heart failure, hemorrhage, hyperlipidemia, and venous thrombosis. These were referred to as risk factors in the CRF and collected in the phase 3 studies. The unadjusted p-value was 0.59 indicating that there was no statistically significant difference in time to death between the Mircera and reference groups (Table 49). In addition, the parameter estimate for the treatment difference did not change after inclusion of baseline risk factors in the model. Risk factors of IHD, peripheral vascular disease, cerebral vascular disease, and congestive heart failure all had an independent effect on death ($p < 0.05$). The relative risk was highest for patients with IHD vs patients without IHD (relative risk of 2.2, $p < 0.0001$).

**Table 49: Overall Survival by Risk Factors
(Cox Regression Analysis, Phase 3 Population)**

Covariate	Variable	Estimate	Relative Risk	95% Confidence Interval	Risk Ratio p-Value
1:NO COVARIATE					
Treatment	RO0503821 vs. Reference	0.0890	1.093	[0.79;1.52]	0.5939
2:MULTIVARIATE					
Treatment	RO0503821 vs. Reference	0.0787	1.082	[0.78;1.50]	0.6396
DIABETES	yes vs. no	0.3173	1.373	[0.98;1.93]	0.0666
ISCHEMIC HEART DISEASE	yes vs. no	0.7741	2.169	[1.53;3.08]	<.0001
PERIPHERAL VASCULAR D.	yes vs. no	0.5774	1.781	[1.25;2.53]	0.0013
ARTERIAL HYPERTENSION	yes vs. no	-0.0277	0.973	[0.52;1.81]	0.9303
CEREBRAL VASCULAR D.	yes vs. no	0.4938	1.638	[1.10;2.43]	0.0144
CONGESTIVE HEART F.	yes vs. no	0.6338	1.885	[1.34;2.66]	0.0003
HEMORRHAGE	yes vs. no	0.1507	1.163	[0.76;1.79]	0.4932
HYPERLIPIDEMIA	yes vs. no	-0.3017	0.740	[0.53;1.03]	0.0770
VENOUS THROMBOSIS	yes vs. no	0.2745	1.316	[0.92;1.89]	0.1367

Phase 3 Studies

In each of the phase 3 studies, crude mortality rates in the Mircera and reference groups were generally similar (Table 50). With Mircera, the mortality rates ranged from 3.6% to 10.0%, a range that appears to be significantly greater than the rate seen with the reference agents (6.0% to 8.6%). The highest mortality rate of 10% was seen with Mircera SC Q2W for anemia correction in non-dialysis patients. The lowest mortality rate of 3.6% was seen with Mircera IV or SC using prefilled syringes for hemoglobin maintenance in dialysis patients. The magnitude of the difference in mortality rate was highest in favor of Mircera (-2.9%) in BA16736 (study medication administered IV), and highest in favor of the reference agents (1.9%) in BA16740 (study medication administered SC).

It remains possible that, for Mircera, IV administration may be safer than SC administration. Although the PK data indicate that the half-life of Mircera is not appreciably dependent on the route of administration, the PD effect may be greater with SC than with IV administration. The greater PD effect may in turn have a significant effect on treatment-related mortality, if: (1) raising the hemoglobin can be associated with treatment-related mortality, and (2) SC Mircera raises the hemoglobin more effectively than IV Mircera when given according to the same dose administration guidelines.

Table 50: Deaths in Controlled Phase 3 Studies

Study	Comments	Mircera		Reference		Mortality Rate Difference (%)
		Patients (N)	Deaths (%)	Patients (N)	Deaths (%)	
BA16736	correction, IV, Q2W, dialysis, epoetin	105	6 (5.7)	35	3 (8.6)	-2.9
BA16738	correction, SC, Q2W, non-dialysis, darbepoetin	50	5 (10.0)	47	4 (8.5)	1.5
BA16739	maintenance, IV, QW and Q4W, dialysis, epoetin	441	34 (7.7)	225	17 (7.6)	0.1
BA16740	maintenance, SC, Q2W and Q4W, dialysis, epoetin	380	31 (8.2)	191	12 (6.3)	1.9

BA17283	maintenance, IV, Q2W, dialysis, darbepoetin	153	13 (8.5)	156	12 (7.7)	0.8
BA17284	maintenance, IV/SC, Q2W, dialysis, PFS, epoetin	165	7 (3.6)	168	10 (6.0)	-2.4
All Studies	NA	1294	96 (7.4)	822	58 (7.1)	0.3

Numbers of patients reflect study period through evaluation (exclude extension period): Mortality Rate Difference = Mircera mortality rate minus reference mortality rate; IV = intravenous; SC = subcutaneous; IV/SC = intravenous or subcutaneous; epoetin = epoetin alfa or beta as reference agent; darbepoetin = darbepoetin alfa as reference agent; PFS = prefilled syringes; NA = not applicable.

Review Comments:

- It is unexpected that the highest mortality rate was seen in the only phase 3 study involving non-dialysis patients (BA16738); mortality rates that appear to be significantly lower were seen in all other phase 3 studies involving dialysis patients (higher risk group relative to non-dialysis patients). It remains unclear whether SC use of Mircera for anemia correction is associated with a greater risk of death than with other combinations of administration route (IV or SC) and previous therapy (anemia correction or hemoglobin maintenance).
- This observation is consistent with the hypothesis that greater treatment risks may be associated with achieving and sustaining higher target hemoglobin levels. Although protocol-specified target hemoglobin levels do not appear to be appreciably different among the six phase 3 studies, an analysis that adjusts for the hemoglobin level over time (i.e., determination of AUC for the hemoglobin response curve) may show that Mircera therapy in BA16738 (anemia correction in non-dialysis patients using SC Mircera dosing) sustained the highest hemoglobin level over time.
- Controlled comparisons within each study and uncontrolled comparisons across the controlled studies suggest that higher doses, SC route, and anemia correction may be associated with higher mortality rates than lower doses, IV route, and hemoglobin maintenance:
 - In BA16736, the mortality rate with Mircera was lower than that with the reference agent when a Mircera dose of when 0.4 ug/kg was used IV.
 - In BA16738, the mortality rate with Mircera was higher than that with the reference agent when a Mircera dose of 0.6 ug/kg was used SC.
 - In BA16739, using Mircera at fixed doses Q2W or Q4W IV resulted in a mortality rate comparable to that seen with the reference agent.
 - In BA16740, using Mircera at fixed doses Q2W or Q4W SC resulted in a mortality rate higher than seen with the reference agent. Although the sponsor claims that Mircera IV and Mircera SC have comparable PK and PD profiles, IV and SC routes may be significantly different, at least with respect to its potential association with mortality and other adverse events. Currently approved erythropoietin products (epoetin alfa, epoetin beta, and darbepoetin alfa) exhibit more prolonged PK profiles and PD responses with SC than with IV dosing, and Mircera may not be an exception.

- In BA17284, using Mircera in pre-filled syringes resulted in a mortality rate lower than that seen with the reference agent. The pre-filled syringes tended to deliver conservative doses of Mircera, in comparison with rigorous weight-based dosing.
- To explore a potential relationship between administration route and mortality, the sponsor should present IV and SC data separately in BA17284. Similarly, separate data analyses for Q2W and Q4W dosing schedules in studies BA16739 and BA16740 will be helpful in confirming the lack of a potential schedule effect.
- A comparison of pooled data (all studies) does not suggest an appreciable difference in the mortality rate between Mircera and the reference agents (7.3% with Mircera vs 7.1% with reference agents).
 - Although the sponsor claims that safety of Mircera is not different from that of the reference agents based on analyses of pooled (and therefore uncontrolled) data, analyses of controlled (individual studies) data may reveal safety differences. The safety differences are likely to be related to the degree of induction of erythropoietic (or other) activity (dose, route, and target hemoglobin), rather than to an effect intrinsic to Mircera.
 - These observations support approval of Mircera with the product label specifying a more conservative dosing in anemia correction (perhaps _____, instead of 0.6 ug/kg as proposed) and in hemoglobin maintenance (hemoglobin target lower than 12.0 g/dL as specified in labeling of approved erythropoietin products). A hemoglobin target of _____ g/dL may be more appropriate than 12.0 g/dL, since _____ g/dL was tested in the CHOIR study whereas as 12.0 g/dL is an arbitrary selection not yet tested in a clinical study.

Deaths by Subgroups

Deaths were examined by the same subgroups used for adverse events. Because the individual causes of deaths were 1% or less in all subgroups, the results below discuss only the overall incidence of death by subgroup. In the phase 3 studies, the frequency of deaths was similar in the Mircera group (6.7%) and in the reference group (6.1%).

- In the anemia correction studies excluding the phase 2 long-term extension, the frequency of deaths was similar and low in the Mircera group (3%) and in the reference group (3%).
- In the hemoglobin maintenance studies excluding the phase 2 long-term extensions, the frequency of deaths was similar in the Mircera group (7%) and the reference group (7%).
- By dose schedule, in the phase 3 hemoglobin maintenance studies, the incidence of deaths was similar in patients who received Mircera Q2W (7%) and patients who received reference (7%), but slightly higher in patients who received Mircera Q4W (8%).
- By route of administration, in the overall population excluding the phase 2 long-term extensions, there was little difference between treatment groups in the incidence of deaths in IV patients (6% Mircera vs 7% reference) or in SC patients (5% both treatment groups). The percentage of deaths was slightly higher in patients who received study treatment IV compared with SC in both groups.
- By dialysis modality in the overall population excluding the phase 2 long-term extensions, the percentages of deaths in patients on hemodialysis and in patients not on dialysis were similar between groups: 6% Mircera vs 7% reference in hemodialysis patients; 2% in both groups in patients not on dialysis. The incidence of deaths was lower in both groups in patients on

hemodialysis compared with patients not on dialysis. In patients on peritoneal dialysis, the incidence of deaths was lower in the Mircera group (2%) than in the reference group (13%). However, the total number of patients in the reference group who were receiving peritoneal dialysis was very small (N = 31); therefore the results should be interpreted with caution for this subgroup.

- By US vs non-US patients in the overall population excluding the phase 2 long-term extensions, the incidence of deaths was higher in US patients than in non-US patients in both treatment groups. The same trend was seen for adverse events in US vs non-US patients. However, there was little difference in the incidence of deaths in the Mircera vs reference group in either US patients (7% Mircera, 8% reference) or non-US patients (5% both treatment groups).
- By gender in the overall population excluding the phase 2 long-term extensions, the frequency of deaths was slightly higher in male patients than in female patients in both treatment groups. In the Mircera group, 6% of male patients died and 5% of female patients died. In the reference group, 7% of male patients and 5% of female patients died.
- By age, in the overall population excluding the phase 2 long-term extensions, the percentage of patients who died was higher in the Mircera group (13%) than in the reference group (10%) in patients > 75 years of age. However, in the other two age categories, the frequency of death was lower in the Mircera group than in the reference group (65-74 years: 7% Mircera vs 9% reference; < 65 years: 3% Mircera vs 4% reference).
- By race in the overall population excluding the phase 2 long-term extensions, there were no trends seen in deaths by race in Caucasian or in Black patients. In Oriental patients, the incidence of deaths was higher in the Mircera group (5%) than in the reference group (2%). However, the total number of Oriental patients was very small (N=85 Mircera; N=60 reference) and the total number of deaths was also low in both groups (4 in Mircera, 1 in reference); therefore the results should be interpreted with caution for this subgroup.
- By weight in the overall population excluding the phase 2 long-term extensions, the incidence of deaths was slightly lower in the Mircera group (4%) than in the reference group (6%) in patients in the weight category =80 kg. In patients in the other two weight categories (<65 kg and 65-<80 kg), the incidence of deaths was similar between groups (7% Mircera, 6% reference in < 65 kg; 6% each group in 65-<80 kg).
- By diabetes at baseline in the overall population excluding the phase 2 long-term extensions, the percentage of deaths was slightly higher in patients with diabetes in both treatment groups. In the Mircera group, 8% of patients with diabetes died and 4% of patients without diabetes died. In the reference group, 7% of patients with diabetes and 5% of patients without diabetes died.
- By cardiovascular disease at baseline, in the phase 3 population, total percentage of deaths in patients with cardiovascular disease at baseline was 7% in the Mircera group and 6% in the reference group. There were too few patients without cardiovascular disease to make a valid comparison in this subgroup.

Sudden Deaths

Table 51 lists the 8 cases of "sudden deaths" as reported by the clinical investigators in phase 2 and phase 3 studies. One of the 8 cases occurred in an uncontrolled phase 2 study. Narrative summaries of the 8 cases follow Table 51.

**Appears This Way
On Original**

Table 51: Sudden Deaths (Safety Population)

Study		Age	Risk Factors	Day	Hemoglobin			
Number	Description				At Baseline	At AE (Day)	Max 2wk	MCh 4wk
BA16286	phase 2, maintenance, SC, dialysis, dose escalation	67	NA	407	12.2	10.8 (381)	NA	NA
BA16739	maintenance, IV, Q2W and Q4W, dialysis, epoetin	85	HTN, CHF, hyperlipidemia, VAT	295	11.45	12.1 (295)	12.1	1.4
BA16739		72	HTN, CHF, NIDDM	20	12.41	13.4 (15)	13.4	1.8
BA16740	maintenance, SC, Q2W and Q4W, dialysis, epoetin	73	HTN, TIA, IDDM, MI, PVD, VAT	55	12.63	12.3 (50)	12.3	1.4
BA17283	maintenance, IV, Q2W, dialysis, darbepoetin	64	HTN, CVA, MI, PVD	341	11.21	11.3 (337)	11.3	-0.3
BA17284	maintenance, IV/SC, Q2W, dialysis, PFS, epoetin	57	HTN, NIDDM, hyperlipidemia, MI	211	12.36	10.8 (211)	10.8	0.5
BA17284		55	HTN, NIDDM, PVD	174	12.42	15.2 (169)	15.2	1.1
BA17284		67	HTN, TIA, CHF, IDDM, hyperlipidemia, angina	84	12.88	13.6 (78)	13.6	2.3

AE = adverse event (sudden death); AE (day) = hemoglobin and day of hemoglobin prior to sudden death; CHF = congestive heart failure; CVA = cerebrovascular accident; Day = study day of sudden death; HTN = hypertension; IDDM = insulin-dependent diabetes mellitus; Max 2wk = maximum hemoglobin within 2 weeks of sudden death; MCh 4wk = maximum change in hemoglobin within 4 weeks of sudden death; MI = myocardial infarction; NA = not available; NIDDM = non-insulin-dependent diabetes mellitus; PVD = peripheral vascular disease; TIA = transient ischemic attack; VAT = vascular access thrombosis

Review Comments on Table 51:

Although the rates of overall and cardiac mortality do not appear to be significantly different between Mircera and reference groups, the data suggest a trend for higher mortality rates with Mircera, as well as a statistically significant imbalance in sudden deaths, or at least in the use of the term "sudden death" in reporting deaths. The apparent imbalance remains unexplained.

Four of the six phase 3 studies were in hemoglobin maintenance in dialysis patients. All of the sudden deaths (including the single phase 2 case) were reported in hemoglobin maintenance in dialysis patients. Five of seven phase 3 cases had a hemoglobin level that exceeded 12.0 g/dL within one week of sudden death. Although the number of patients is small, these observations raise the following considerations in evaluating the safety of erythropoietin therapy in renal anemia:

- At hemoglobin levels above baseline, higher hemoglobin levels are less safe than lower levels.
- Patients with more severe CRF are at greater risk than those with less severe CRF.
- For an erythropoietin product, a longer circulating half-life may be less safe than a shorter one.

Although anemia correction is an unstable situation than hemoglobin maintenance (hemoglobin level rises over time), the relatively low hemoglobin level at initiation of anemia correction may serve as a "safety buffer" before the hemoglobin level rises to levels that place the patient at significant risk for sudden deaths. Mircera may be less safe than the reference erythropoietin products, not because of an intrinsic difference in product safety, but because of its prolonged circulating half-life places the patient at an increased risk of exceeding the "safe" hemoglobin level, particularly with SC dosing.

A closer examination of the Mircera regimens used (dose, interval, route), the baseline disease status (severity of CRF, risk factors for sudden deaths, baseline hemoglobin), and the treatment duration may be helpful in investigating these concerns.

Narrative Summaries

Case 1

Patient 30347/4606 enrolled in phase 2 study BA16286: dose escalation study for hemoglobin maintenance in dialysis, Mircera 128.9 ug SC Q4W

67 year-old black male with CRF (diabetes and hypertension) had been receiving hemodialysis for approximately one year. An SAE of sudden death was reported on **day 407** of BA16286. The patient awoke and got out of bed and then collapsed. Paramedics were called but the patient was dead on their arrival. The sudden death was assessed as not related to study drug. There was no autopsy and the death certificate is not available. An investigator comment in the clinical database noted that the "patient experienced sudden unexplained death at home." The Dialysis Discharge Summary and ESRD Death Notification Form report that the patient died at home of natural causes. According to the patient's primary care physician, cause of death is stated as "natural causes."

Additional information about the death comes from the clinical database, the SAE report, and source documentation from the investigative site. The source documentation includes the dialysis center discharge summary, ESRD death notification form, dialysis logs and lab reports, and records from hospitalization for SAE of dyspnea (discharge summary, laboratory and radiology reports).

- Comments pertaining to the death in the SAE report reference a non-serious AE of chest discomfort and an SAE of dyspnea reported on **day 399**. The onset of dyspnea occurred on day 398; by day 399 the dyspnea had worsened and the patient complained of chest pressure (7 on a 10 point scale). Aspirin and sublingual nitroglycerin were given en route to the hospital. Chest pressure decreased but shortness of breath continued until a lisinopril drip was given (for one day). Treatment was also started with captopril and oxygen, and an electrocardiogram and

chest X-ray were performed. On day 400 oxygen was stopped. During the hospitalization the patient was monitored on telemetry; there were no cardiac events and a myocardial infarction was ruled out with serial cardiac enzymes. On day 402 the severe shortness of breath (dyspnea) resolved and there was no chest pain. At the patient's final dialysis treatment (**day 404**) the vital signs were: pre-dialysis, BP 168/79 and heart rate 90; post-dialysis, BP 194/84 and heart rate 92. There were no complaints post dialysis.

- Additional information from the patient's medical record notes that the ECG done during hospitalization did not show any relevant changes, while chest X-ray showed cardiomegaly, vascular congestion and signs of interstitial and alveolar pulmonary edema compatible with congestive heart failure. The maximal troponin I was < 0.4 ng/mL, maximal CK was 85 U/L).
- The reported past medical history included congestive cardiomyopathy, depression, diabetes mellitus, diabetic gastropathy, hypercholesterolemia, hypertension, hypotension, allergies to iodine and other chemicals, drug hypersensitivity and peripheral vascular disease.
- The randomized starting dose of Mircera was 66 ug SC Q4W (screening hemoglobin 12.2 g/dL), which was maintained until **day 227**. The dose was increased (3 times) to: 82.5 ug (hemoglobin 11.2 g/dL) on **day 227**, 103.1 ug (hemoglobin 10.6 g/dL) on **day 309**, 128.9 ug (hemoglobin 11.5 g/dL) on **day 372**. The last dose of study drug was 128.9 ug on **day 393**.
- On **day 400** there were two non-serious adverse events reported: an exacerbation of chronic sinusitis for which the patient received computerized tomography of the head (results not reported) and a furuncle behind the left ear which was lanced and treated with antibiotics. The sinusitis was reported as unresolved and the furuncle as resolved without sequelae on **day 404**. Additional information from the SAE report indicate that the patient complained of nasal discharge with foul smell and taste (non-serious). Additional information from the patient medical record show that a head CT scan was performed to evaluate exacerbation of chronic sinusitis, which showed residual chronic inflammation. Hemoglobin levels were 9.7 g/dL and 9.6 g/dL on **days 401 and 402**. White blood cell count was 20,600/ μ L, 12,600/ μ L and 11,500/ μ L on **days 400, 401 and 402**. Blood cultures were negative. The SAE of sudden death occurred on **day 407**. Additional earlier hemoglobin measurements were (g/dL): 10.6 (**day 297**), 11.3 (**day 325**), 11.5 (**day 360**), and 10.8 (**day 381**).

Review Comments on Case 1:

The time course of this patient's history shows that the patient's hemoglobin was resistant to Mircera treatment; the hemoglobin appears to have repeatedly drifted back down towards "baseline" despite escalating doses of Mircera in the attempt to raise the hemoglobin to a level significantly above "baseline." Dyspnea and chest pain occurred on day 399 following the third and final increase in Mircera dose (on day 372, from 103.1 ug to 128.9 ug) to further increase the hemoglobin of 11.5 g/dL.

It remains unknown whether the observed treatment resistance reflects insufficient stimulation of erythropoiesis or increased red cell destruction in association with increased erythropoiesis. At stable hemoglobin levels ("steady-state" hemoglobin maintenance levels), higher levels are expected to be associated with higher levels of red cell turnover than are lower levels, and high levels of red cell turnover may predispose patients to a thrombotic state. Further, rheological properties of blood may be optimal a hematocrit of about 30% (10 g/dL hemoglobin). These

considerations suggest that anemia of renal failure may be a desirable adaptive response, rather than an undesirable disease sequelae.

Over at least one week period preceding the patient's sudden death, the patient's blood pressure was not controlled (day 404 post-dialysis BP of 194/84 and heart rate 92) and the patient had chronic sinusitis and skin infection (furuncle behind left ear). Over this time period, the hemoglobin level decreased from 11.5 g/dL to 9.6 g/dL.

The patient's history raise a concern about the role of Mircera in exacerbating hypertension and in increasing the risk of thrombosis. In this patient, uncontrolled hypertension in combination with infection may have been significant contributors to sudden coronary thrombosis, malignant cardiac arrhythmias, and sudden death. The dose of Mircera given SC Q4W appears to be high; the patient's weight should be reported to permit weight-adjusted dose analysis.

Case 2

Patient 40335/2555 enrolled in phase 3 study BA16739: hemoglobin maintenance in dialysis, Mircera 105.5 ug IV Q4W

85 year-old black male with CRF (hypertension, large vessel disease) had been receiving hemodialysis for approximately 15 months. On **day 295**, an SAE of sudden death at home was reported. The event was not treated. No autopsy was performed. The cause of death was noted as sudden death. The death was assessed as not related to study drug.

Information from the clinical database indicates that the patient had completed the week 43 study visit (including dialysis session) on the same day as the death. An investigator comment on the Case Report Form notes that the patient had no complaints and completed an uneventful dialysis session. He ambulated from the dialysis center, drove himself home, and lay down in bed, where he was found expired by a family member later that day. The death was reported to the center by a social worker who had worked with the family. The investigator confirmed the assessment of the death not being related to study drug, and suggested that possibly there was a silent myocardial infarction and/or arrhythmia during sleep.

Additional information about the death was obtained from the clinical database, clinical scientist visit to the investigative site, and source documentation. The source documentation includes records of a prostate cancer episode about 10 years prior, echocardiogram results 1-2 years prior, documentation from dialysis sessions and clinical research encounter forms for the course of study; cardiology consult/pacemaker follow-up, H&P from new primary care MD; surgery/anesthesia/radiology records from various vascular access procedures; ECG reports, and administrative documents.

- The past medical history included hypertension, hyperlipidemia, vascular access thrombosis, congestive heart failure (NYHA class I), sinus bradycardia, trifascicular block (pacemaker user), mitral valve incompetence, aortic atherosclerosis, peripheral neuropathy, herpes zoster, hepatic artery stenosis, and gout. Information from the site visit included confirmation by the investigator of the following key risk factors: hyperlipidemia with aortic atherosclerosis, congestive heart failure, hypertension with moderate mitral valve regurgitation, and atrial fibrillation. Concomitant medications included isosorbide mononitrate, hydralazine, sevelamer, allopurinol, quinine sulfate, calcitriol, heparin and ferrous gluconate.
- The mean screening hemoglobin was 11.4 g/dL. At baseline the patient was receiving 3000 IU of epoetin alfa IV TIW. He was randomized to receive 200 ug of Mircera IV Q4W, which was

maintained until **day 57**. Between **days 57 and 141** there were three per protocol dose reductions followed by a per protocol dose increase to 105.5 ug on **day 281** (last dose level).

- There were two non-serious AEs of arteriovenous graft thrombosis, both assessed as not related to study drug. The first was on **day 8**, treated with angioplasty and resolved with sequelae after 113 days. The second was on **day 143**, treated with thrombolysis, venous catheterization, AV fistula creation, and catheter removal and resolved without sequelae after 83 days. There were no additional AEs. The last four hemoglobin measurements were (g/dL): 10.8 (**day 253**), 11.9 (**day 267**), 10.7 (**day 281**), and 12.1 (**day 295**).
- The patient was diagnosed with prostate cancer approximately 10.5 years prior to study entry (prostate ultra-sound and needle biopsy). The disease was localized, and the patient was treated with radiation and hormone therapy and was assessed as disease-free at study entry.
- There is a cardiology report from a routine pacemaker evaluation dated approximately 1 week prior to the patient's death which indicates that the pacemaker was functioning well.
- Monthly dialysis summaries and nutrition notes indicate a gradual decline in serum albumin (3.7 - 3.4 mg/dL) over the course of the study.
- The report from the primary care physician (dated 2 weeks prior to the death) notes patient complaint of fatigue and mild lack of appetite during the past 6 months. There were no complaints of chest pain or shortness of breath. The physician's impression was that fatigue was a combination of co-existing, known medical factors included chronic anemia, CRF and cardiac disorders.

Review Comments on Case 2:

The time course of this patient's history shows that the patient's hemoglobin was responsive to Mircera treatment. AV graft thrombosis occurred twice after switching erythropoietin therapy from epoetin alfa to Mircera at a dose which proved to be too high. The narrative summary does not document good control of hypertension. There is no indication that the patient was infected near time of sudden death. This patient's history leading up to sudden death is notable for excessive Mircera dose (requiring dose reductions), hemoglobin levels well below the intended target when Mircera was given Q4W, AV graft thromboses, and dialysis performed on the day of sudden death.

In addition to the concerns noted in Case 1 about the safety of Mircera, Case 2 suggests that good treatment response (to hemoglobin levels above 12 g/dL) and intermittent "excessive" treatment may be risk factors for sudden coronary thromboses, malignant cardiac arrhythmias, and sudden death. Intermittent "excessive" treatment may be expected to occur more frequently with prolonged (Q4W) dosing intervals. Further, the exposure to the extracorporeal circuit during hemodialysis may be expected to activate the complement system, trigger a generalized inflammatory state, and establish a clinical setting in which excessive erythropoietin therapy is particularly likely to cause sudden thrombosis.

Case 3

Patient 40390/0102 enrolled in phase 3 study BA16739: hemoglobin maintenance in dialysis, Mircera 200 ug IV Q4W

72 year-old black female with CRF (diabetes and hypertension) had been receiving hemodialysis for approximately 4.2 years. On **day 20**, the patient was found dead in bed at home. There was

no autopsy; the sudden death was assessed as not related to study drug. The underlying causes of death were reported as coronary artery disease and diabetes. The Nephrology Division Death Summary from the study site reports the immediate cause of death was sudden death at home; comorbid conditions contributing to death were indicated as coronary artery disease and diabetes mellitus; the death was not expected.

Comments on the Case Report Form, SAE report and physician progress notes indicate that on the day of the event (**day 20**) the patient went home after hemodialysis and spent a usual afternoon and evening at home. She had been sitting and watching television; when the patient's niece went to wake her she found that the patient had died. The physician progress notes report that the patient received 3 units of humulin approx 1.5 hrs prior to end of dialysis because of blood glucose of 21 mmol/L (patient regularly received intra-dialytic parenteral nutrition during dialysis); glucose was 22.6 at discharge, following discontinuation of parenteral nutrition; 3 kg were removed during the last dialysis session (dialysis records indicate that pre-dialysis weights were generally about 2-3 kg above dry weight indicating fluid overload during most dialysis treatments); vital signs were stable and there were no signs/symptoms.

Additional information about the death comes from the clinical database, the SAE report, the clinical scientist site visit, and source documentation. The source documentation includes the nephrology division death summary, physician progress notes, dialysis records from the screening and study treatment period, and a hospital admission note from approximately 4.5 years prior to study entry.

- Relevant cardiac history: The screening ECG from the clinical database revealed left bundle branch block and prolonged QTc. Information obtained from the site visit indicates that the patient had dilated cardiomyopathy with an ejection fraction of about 25%. A previous coronary angiogram had not shown critical stenosis of coronary arteries.
- Past medical history included NIDDM, hypertension, congestive heart failure (NYHA class II), asthma, left bundle branch block, and hypothyroidism. Concomitant medications included calcitriol, calcium carbonate, iron sucrose, levothyroxine, tolbutamide, warfarin, paracetamol, and salbutamol.
- The mean screening Hb was 12.6 g/dL. At baseline the patient was receiving epoetin alfa, 3000 IU, IV TIW. She was randomized to receive Mircera 200 ug IV Q4W. The patient received one dose of study drug. There were no other adverse events recorded. The last four recorded Hb measurements were (g/dL): 11.6 (day -7), 11.8 (day 1), 12.0 (day 8), and 13.4 (day 15). Additional information from the source documentation includes the following:
 - The patient did not have a prolonged period of poor nutritional intake prior to the death.
 - Physician notes from 4 weeks prior to screening mention left ventricular ejection fraction of about 20% with significant left ventricular dysfunction; chest x-ray showed global cardiac dysfunction; ECG sinus rhythm
 - Hospital admission notes from approximately 4.5 years prior to study start, when patient developed irreversible renal failure and initiated dialysis, confirms long-term history of asthma and multiple episodes of congestive heart failure. Reported ECG abnormalities were consistent with those identified during screening.

Review Comments on Case 3:

The time course of this patient's history shows that the patient's hemoglobin was responsive to Mircera treatment; the hemoglobin level rose to 13.4 g/dL on day 15 after receiving just one dose intended to be given on a Q4W regimen. The narrative summary does not document good control of hypertension. There is no indication that the patient was infected near time of sudden death.

This patient's history leading up to sudden death is notable for an excessive Mircera dose eliciting a hemoglobin response well above the intended target and dialysis performed on the day of sudden death. In addition to the concerns noted in the two cases described above about the safety of Mircera, Case 3 suggests that, in addition to establishing a generalized inflammatory state, hemodialysis predisposes to thromboses in erythropoietin treatment by effecting rapid fluid removal and hemoconcentration. Among others, sudden hemoconcentration (and potentially sudden changes in electrolyte balance) may be yet another risk factor to consider in choosing erythropoietin treatment regimens: a larger safety margin may be necessary (smaller dose, more frequent dosing interval, lower hemoglobin target) in dialysis than in non-dialysis.

Case 4

Patient 39138/2207 enrolled in phase 3 study BA16740: hemoglobin maintenance in dialysis, Mircera 60 ug SC Q2W

73 year-old Caucasian male with CRF (diabetes) had been receiving hemodialysis for approximately 2.5 years. Sudden death was reported on day 55. There was no treatment and no autopsy. The death was assessed as not related to study drug. Investigator comments on the patient's case report form mention that no findings (e.g., electrocardiogram, enzyme measurements, etc) were available to establish a diagnosis for the sudden death, and that the patient had died during breakfast and was not hospitalized at the time.

Information from the site visit noted that two months before study start, echocardiography revealed signs of coronary artery disease, left ventricle hypertrophy with mild heart wall hypokinesis, global mild to moderate decrease of left ventricle contractility, left and right atrial enlargement, signs of valvulopathy (mild aortic insufficiency and mild mitral insufficiency), and chest X-ray revealed blood flow inversion due to pulmonary circulatory overload and heart enlargement.

Information from the source documentation confirms the echocardiography and chest X-ray findings reported above and reports ECG findings: sinus bradycardia, left axial deviation, non-specific intraventricular block, T wave abnormality and possible lateral ischemia. Post-dialysis systolic blood pressure was greater than 160 mmHg during the 3 weeks prior to the event.

Additional information about the death comes from the clinical database, the clinical scientist site visit, and source documentation. The source documentation is translated from Italian into English and includes a discharge summary from hospitalization approximately 2 months prior to study screening for AV fistula thrombosis and lab values from days 1-50 of the study.

- Past medical history included IDDM, myocardial infarction, amputation, transient ischemic attack, vascular access thrombosis, hypertension, and bundle branch block. Concomitant medications included insulin, heparin, omeprazole, pentoxifylline, amiodarone, warfarin, sodium polystyrene sulfonate, calcium carbonate, enalapril, and ferrous gluconate.
- The mean screening Hb was 12.63 g/dL. At baseline the patient was receiving epoetin beta 2000 IU, SC, BIW. He was randomized to receive Mircera 60 ug SC Q2W. There were no dose adjustments or deviations. The last dose of study drug was 60 ug on day 43. There were

no other adverse events. Reported hemoglobin measurements were (g/dL): 12.5 (day 1), 12.6 (day 8), 12.5 (day 15), 12.5 (day 22), 11.7 (day 29), 10.9 (day 36), 11.9 (day 43), and 12.3 (day 50).

Review Comments on Case 4:

The narrative summary suggests inadequate control of hypertension during the study. There is no indication that the patient was infected near time of sudden death. The summary does not state when the patient was last dialysed prior to sudden death. No new safety concerns are noted in this case summary.

Case 5

Patient 39430/5402 enrolled in phase 3 study BA17283: hemoglobin maintenance in dialysis, Mircera 100 ug IV Q2W

This 64-year-old Caucasian male with CRF (hypertension) had been receiving hemodialysis for approximately 5 months. Sudden death was reported at home on day 341 of unknown cause. There was no autopsy. The death was assessed as not related to study drug. During the site visit the investigator stated that in his opinion the patient died as consequence of his cardiac disease and that the death was probably due to an "electrical event." The patient's case report form in the clinical database notes that the systolic blood pressure (pre-dialysis and post-dialysis) was < 100 mmHg 4 days prior to the death (day 337). Potassium levels during the study ranged from 5.8 – 6.5 mmol/L except on day 85 when it was 4.6 mmol/L.

Information obtained at the site visit indicates that the patient experienced asystole at about 8:15 PM. Emergency service was called and cardiopulmonary resuscitation was initiated. The patient experienced electromechanical dissociation, ventricular tachycardia and was defibrillated. The patient did not recover a normal pulse. At 9 PM, he was admitted to the emergency department and again experienced electromechanical dissociation and ventricular tachycardia; he was defibrillated and again experienced EMD. The patient did not recover and was declared dead at 10 PM. No autopsy was performed following the wish of the patient's family. Additional information about the death comes from the clinical database and the clinical scientist site visit. There is no source documentation for this patient.

- Approximately 18 months prior to the death, coronary angiography revealed multiple important stenoses of the coronary vessels. At around the same time echocardiography revealed left ventricular dilatation and posterolateral aneurysm. The ejection fraction was 39% with severe dilatation of the left atrium and slightly enlarged mitral valve. The patient had a history of underlying cardiac disease for at least 8 years prior including atrial fibrillation, left cardiac insufficiency, ventricular dilatation, left atrial aneurysm, left ventricular hypertrophy, mitral insufficiency, and concentric inferoposterolateral akinesia. Blood pressures on day 339 (2 days prior to the death) were 108/67 at 8:15 AM, 119/78 at 10:15 AM, and 106/69 at 11:15 AM.
- Past medical history included myocardial infarction, intermittent claudications, thrombotic stroke, hypertension, paroxysmal atrial fibrillation, and renal cell carcinoma. Concomitant medications included amiodarone, aspirin, carvedilol, clopidrogel, digoxin, isosorbide mononitrate, calcium acetate, iron sucrose, and enoxaparin.

- The mean screening Hb was 11.2 g/dL. At baseline the patient was receiving darbepoetin 70 ug IV QW. He was randomized to receive Mircera 100 ug IV Q2W, which was maintained until **day 71**. The dose was reduced 3 times per protocol between **days 71 and 225**. The last dose of study drug was 42.2 ug on day 337.
- The only other adverse events reported were SAEs, assessed as not related to study drug. On **day 3**, there was an SAE of fever of unknown origin, not treated, and resolved without sequelae after 9 days. On **day 80** there was an SAE of rectal hemorrhage. The patient received a colonoscopy which identified the bleeding source as an internal hemorrhoid. There was no treatment and the event resolved without sequelae after three days. The final four Hb measurements were (g/dL): 11.8 (**day 295**), 12.2 (**day 309**), 11.6 (**day 323**), and 11.3 (**day 337**).

Review Comments on Case 5:

This narrative summary is notable for sudden death in a setting of renal cell carcinoma and severe cardiovascular disease which includes ventricular aneurysm, in addition to CRF. The mechanism of sudden death in this patient is likely to be different from that in other patients described above.

Hypertension appears not to have been a concern; the patient's compromised cardiac function may have been insufficient to generate hypertensive blood pressures. There is no indication that the patient was infected near time of sudden death. The summary does not state when the patient was last dialysed prior to sudden death. No new safety concerns are noted in this case summary.

Case 6

Patient 44157/9387 enrolled in phase 3 study BA17284: hemoglobin maintenance in dialysis, Mircera (prefilled syringe) 100 ug SC Q2W

57 year-old Asian male with CRF, diabetes, neoplasm, and nephrectomy had been receiving hemodialysis for approximately 6 years. Sudden death was reported on **day 211**. Resuscitation efforts included epinephrine, lidocaine, sodium bicarbonate, amiodarone, sodium chloride atropine and cardioversion. The sudden death was assessed as not related to the study drug. The underlying cause of sudden death was unknown. The pre-dialysis blood pressure on the day of the event (**day 211**) was 94/51; the patient was taking antihypertensive medication. Two weeks prior the pre-dialysis blood pressure was 143/80.

An autopsy was performed. The autopsy report (see below) notes that during dialysis the patient became increasingly lethargic and lost consciousness; a "code 500" was called and resuscitation was started. The patient was transported to the hospital emergency department, where continued resuscitation attempts were unsuccessful. The autopsy report attributes the death to severe cardiovascular disease which likely caused cardiomyopathy and congestive heart failure. The end result of this process was likely a terminal myocardial infarct and/or arrhythmia. Contributing factors to the death "undoubtedly" included end stage renal disease and severe atherosclerotic and hypertensive peripheral vascular disease. The death certificate listed ventricular arrhythmia and cardiomyopathy as the immediate cause of death with the underlying cause of death as end stage renal disease. Additional information about the death comes from the clinical database and source documentation. The source documentation consists of the full autopsy report and the death certificate.

- Relevant cardiac history: The screening ECG in the clinical database revealed ventricular premature complexes, sinus tachycardia (105 bpm); depressed ST segment and inverted T

waves. On **day 197**, ECG revealed first degree AV block, left anterior hemiblock; depressed ST segment and inverted T waves.

- Past medical history included NIDDM, myocardial infarction, retroperitoneal hemorrhage, vascular access hemorrhage, arterial hypertension, hyperlipidemia, sleep apnea syndrome, gout, Kawasaki's disease, cardiomyopathy, diabetic neuropathy, generalized pruritus, dyspnea, asthenia, spinal column stenosis, drug hypersensitivity (minoxidil, lipitor, iron dextran) and obesity. Concomitant treatments included sevelamer, sodium bicarbonate, colchicine, digoxin, gabapentin, diphenhydramine, paricalcitol, clopidogrel, pantoprazole, glucosamine, chondroitin sulfate, aspirin, ibuprofen, amoxicillin, heparin, zolpidem, carvedilol, and intermittent positive pressure breathing.
- Autopsy report: aneurysmal dilatation and severe calcific atherosclerosis of the coronary arteries, aneurysmal dilatation of the cerebral vessels, dilated cardiomyopathy with multiple old left ventricular infarcts/ischemia; severe calcific atherosclerosis of the aorta, and severe peripheral atherosclerosis—all supporting clinical history of Kawasaki disease. Additional findings included incidental papillary carcinoma of thyroid (0.7 cm greatest dimension), benign prostatic hyperplasia, parathyroid hyperplasia, hepatic congestion, fibrosis, and steatosis, and bilateral pulmonary congestion and edema.
- Mean screening hemoglobin was 12.53 g/dL. At baseline the patient was receiving a weekly dose of 12800 IU epoetin alfa SC and was randomized to receive 100 ug Mircera Q2W. There were 4 per protocol dose escalations between **days 85 and 197**. The last dose escalation from 187.5 ug to 234 ug was on **day 197** (hemoglobin 10.7 g/dL). There were no blood transfusions.
- On **day 176** there was an SAE of supraventricular tachycardia, assessed as not related to study drug, treated with potassium chloride and resolved without sequelae. Additional information from the SAE report in the sponsor's drug safety database notes that an ECG showed possible ectopic atrial tachycardia with occasional premature ventricular complexes, left axis deviation and non-specific ST abnormalities. A portable chest x-ray showed moderate pulmonary vascular congestion, mild edema and mild left basilar atelectasis. An ECG performed the following day (**day 177**) revealed atrial rhythm with first degree a-v block with occasional premature ventricular complexes and non-specific extraventricular conduction delay. Another ECG indicated atrial rhythm with first degree AV block with premature ventricular complexes, anteroseptal infarct of an undetermined age, prolonged QT interval or TU fusion. Premature ventricular complexes were no longer present, however, aberrant conduction was now present. A chest x-ray revealed mild cardiomegaly, central pulmonary venous congestion with mild infiltrates. One day later (**day 178**), the supraventricular tachycardia was considered resolved. The ECG showed atrial rhythm with 1st degree atrioventricular block and premature ventricular complexes.
- On **day 87** there was a non-serious, non-study drug-related AE of arteriovenous fistula site hemorrhage, treated with pressure dressings and resolved after 40 days. On **day 101** there was a non-serious, non-study drug-related AE of dyspnea, which was treated with oxygen, and remained unresolved. On **day 151**, there was a non-serious, non-study drug related AE of upper respiratory infection, which was treated with cefadroxil, and resolved without sequelae. There were no other relevant adverse events. The last four reported hemoglobin measurements were (g/dL): 10.7 (**day 190**), 10.7 (**day 197**), 10.3 (**day 204**), 10.8 (**day 211**).

Review Comments on Case 6:

This narrative summary is notable for sudden death at end of hemodialysis in a setting of severe cardiovascular disease, CRF, anemia treated with escalating doses of Mircera, and pneumonia. Hypertension appears not to have been a concern. As in other summaries above, this summary suggests that hemodialysis (complement and platelet activation, sudden hemoconcentration, potential electrolyte balance) and infection (activation of homeostatic mechanisms, including hemostasis) are risk factors for sudden death that are more important than currently appreciated in increasing the risk of erythropoietin therapy, particularly potential over-treatment using a long-acting preparation.

Case 7

Patient 44164/9303 enrolled in phase 3 study BA17284: hemoglobin maintenance in dialysis, Mircera (prefilled syringe) 100 ug IV Q2W

A 55 year-old Asian man with CRF (diabetes) had been receiving hemodialysis for approximately 3 years. Sudden death at home was reported on **day 174**; the patient was found dead in bed by his brother. Resuscitation was unsuccessful. No autopsy was performed. The sudden death was assessed as not related to the study drug.

The mortality review sheet from the dialysis center indicates cardiac arrest, cause unknown and hyperkalemia as the final diagnosis. Potassium values reported to the clinical database during the study were 4.9, 5.3, 4.6, and 5.3 mmol/L at screening and on **days 29, 85, and 141**, respectively, (normal range 3.5-5.5 mol/L). There is another value of 5.3 mmol/L for study **day 172** reported in the mortality review document. There is a note in the mortality review sheet which suggests that the patient's primary physician considered the death to be related to coronary artery disease and possible arrhythmia/potassium abnormalities. The last dialysis session on **day 172** was reportedly uneventful.

Additional information about the death comes from the clinical database, the clinical science site visit, and source documentation. The source documentation includes the mortality review sheet from the dialysis center and dialysis treatment notes for approximately 1 month prior to death.

- The clinical database indicates that the bilateral bundle branch block noted below in the patient's past medical history was composed of right bundle branch block and left anterior fascicular block. Information from the site visit confirmed hemoglobin values prior to the event and that the patient was diabetic with a history of hypertension, retinopathy, toe amputation and bilateral bundle branch block. Information from the dialysis treatment notes in the source documentation indicates that the last dialysis session was on **day 172**. Hemoglobin was 14.5 g/dL and the patient had no complaints. There were occasional episodes of post-dialysis hypotension. Due to hyperphosphatemia (7.0 mg/dL), phosphate binder treatment was intensified.
- Past medical history included NIDDM, peripheral vascular disease resulting in amputation, arterial hypertension, bilateral bundle branch block, hyperphosphatemia, diabetic retinopathy and hyperparathyroidism. Concomitant treatments included sevelamer, calcium carbonate, folic acid, doxercalciferol, influenza virus vaccine, heparin, and calcium acetate.

Mean screening hemoglobin was 12.33 g/dL. At baseline the patient was receiving a weekly IV dose of 13800 IU epoetin alfa, and was randomized to receive 100 ug Mircera IV Q2W. There were four per protocol dose adjustments between **days 43 - 71**, a per-protocol dosing interruption

for a hemoglobin of 14.3 g/dL (day not specified), a dose reduction 75 ug for a hemoglobin of 13.2 g/dL (day 141), and a dose held for a hemoglobin of 15.2 g/dL (day 169). The last dose of Mircera was 75 ug on day 155. There were no blood transfusions.

There was one non-serious AE of hyperkeratosis (day 83), not related to study drug, treated with vancomycin, and resolved without sequelae. There were no other adverse events. The last four reported hemoglobin measurements were (g/dL): 14.1 (day 148), 14.3 (day 155), 15.1 (day 162), and 15.2 (day 169).

Review Comments on Case 7:

This narrative summary is notable for sudden death two days after hemodialysis in a setting of severe cardiovascular disease, CRF, anemia treated excessively with Mircera. The history is not suggestive of an on-going infection at time of sudden death. Hypertension appears not to have been a concern. As in other summaries above, this summary suggests that hemodialysis (complement and platelet activation, sudden hemoconcentration, potential electrolyte balance) is an important risk factor for sudden death, particularly when renal anemia is treated excessively using a long-acting preparation (hemoglobin levels: 14.1 g/dL on day 148, 14.3 g/dL on day 155, 15.1 g/dL on day 162, and 15.2 g/dL on day 169).

Case 8

Patient 44186/1103 enrolled in phase 3 study BA17284: hemoglobin maintenance in dialysis, Mircera (prefilled syringe) 75 ug IV Q2W

A 67 year-old Caucasian woman with CRF (diabetes, hypertension) had been receiving hemodialysis for approximately 4.5 years. Sudden death was reported on day 84. The cause of death was unknown. No treatment was initiated and no autopsy was performed. The sudden death was assessed as not related to the study drug.

Additional information about the death comes from the clinical database, the SAE report, the clinical scientist site visit, and source documentation. The source documentation consists of 3 pages: a letter from the attending physician, and a copy of the ENT consult noted below.

- Information in the clinical database notes that on day 83 the patient's post-dialysis systolic BP was 192 mmHg and heart rate was 122. On day 79 the systolic BP was 179 mmHg both pre- and post-dialysis. A comment in the SAE report indicates that the patient had had a high fever (38.9°C) on days 82 and 83, and was receiving prednisone. Information obtained at the site visit notes that on day 68 the patient developed sudden hearing loss in the left ear. She was seen by an ENT specialist who prescribed high dose prednisone and had scheduled an MRI. The fever was reported to be 102°F at home, but the patient was afebrile in dialysis. She had an uneventful dialysis run, after which she became very weak and could not get out of bed. The patient was found dead at home on day 84.
- The letter from the attending physician notes that on day 83 the patient came to dialysis with complaints of fatigue, myalgias and cough, consistent with viral upper respiratory infection (reported as non-serious AE). She continued to feel unwell after she returned home and died at home the next day.
- Past medical history included IDDM, angina pectoris, transient ischemic attack, gastrointestinal hemorrhage, other hemorrhage, arterial hypertension, hyperlipidemia, congestive heart failure

(NYHA class III), hypothyroidism, atrial flutter/fibrillation, heart valve insufficiency, diabetic retinopathy, aortic atherosclerosis, drug hypersensitivity (penicillin), intervertebral disc degeneration, erythema (lower leg), and gastrointestinal carcinoma. Concomitant treatments included warfarin, nifedipine, omeprazole, telmisartan, nadolol, digoxin, calcium carbonate, levothyroxine, insulin, heparin, alteplase, and influenza virus vaccine.

- Mean screening hemoglobin was 12.9 g/dL. At baseline the patient was treated with a weekly IV dose of 7000 IU epoetin alfa, and was randomized to receive 60 ug Mircera Q2W. On **day 29** the dose was increased to 75 ug for a hemoglobin of 11.3 g/dL. The last dose of Mircera was 75 ug on **day 71**.
- Throughout the study, there were 5 non-serious AEs, all assessed as not related to the study drug: hypoglycemia treated with juice (resolved) (**day 36**), nausea (resolved without treatment) (**day 59**), sudden hearing loss treated with prednisone and pantoprazole (unresolved) (**day 68**), viral upper respiratory tract infection without treatment (unresolved) (**day 83**), tachycardia of unknown etiology (pre-and post-dialysis heart rates were 122 and 59 bpm, respectively), resolved without sequelae after hemodialysis (**day 83**). The last four reported hemoglobin measurements were (g/dL): 12.0 (**day 57**), 11.3 (**day 64**), 12.5 (**day 71**), and 13.6 (**day 78**).
- The letter from the attending physician confirmed the patient's long-term history of chronic disease including NIDDM (> 30 years) and hypertension (>20 years). The year prior to entry into study BA17284 the patient developed transient left sided numbness and weakness in association with atrial fibrillation which was treated with digoxin and coumadin. Also in that year the patient was found to have multiple polyps on colonoscopy (tubular adenoma with high grade dysplasia and microscopic invasive adenocarcinoma), which were excised and considered cured. The letter notes that the patient was in her usual state of health until the AE of hearing loss on **day 68** noted above.

Review Comments on Case 8:

This narrative summary is notable for sudden death one day after hemodialysis, in association with fever (102 F, presumed upper respiratory infection). Hypertension appears to have been controlled. As in other summaries above, this summary suggests that hemodialysis (complement and platelet activation, sudden hemoconcentration, potential electrolyte balance) and infection are important risk factors for sudden death.

Anemia correction to a hemoglobin level of 12.0 g/dL may have placed this patient to a risk of sudden hemoconcentration to a significantly higher hemoglobin level at dialysis. In this patient with underlying cardiovascular disease, on-going infection, and dialysis-induced activation of homeostasis/hemostasis, the partial elimination of the hemoglobin "safety buffer" (partial correction of renal anemia) through Mircera treatment may have increased the risk of sudden death.

Summary of Review Comments (All Narratives and **Table 51**):

The 8 narratives and **Table 51** above suggest that the risk of sudden death may be increased when the following factors are present in treating renal anemia using an erythropoietin product:

- Hemoglobin maintenance therapy (as opposed to anemia correction)
- Excessive erythropoietin treatment, as evidenced by:
 - Brisk hemoglobin response that results in hemoglobin overshoot
 - Difficulty in increasing the hemoglobin level to a desired level

- Hemodialysis
- Infection
- Uncontrolled hypertension
- Underlying conditions that increase thrombotic risk, including cancer

A slightly increased risk of coronary thrombosis, acute myocardial infarction, malignant cardiac arrhythmias, and sudden death may be expected with hemodialysis, infection, uncontrolled hypertension, or underlying conditions that predispose to thrombotic risk, including cancer. In the setting of erythropoietin therapy for renal anemia, these conditions are routinely encountered, and excessive erythropoietin therapy appears to increase the baseline risk. The increase in risk appears to be greater in hemoglobin maintenance than in anemia correction; in anemia correction, the baseline anemia may serve as a "safety buffer" against excessive treatment. The use of long-acting preparations (such as Mircera), particularly when administered at infrequent intervals (such as Q4W) using high doses and by SC injection (prolonged effect, in comparison with IV route) may magnify the risk of excessive treatment.

An imbalance in the incidence of sudden deaths was observed between Mircera and reference treatments: 7 cases with Mircera versus none with reference agents in controlled phase 3 studies using 1:1 or 2:1 Mircera-to-reference agent allocation. The observed imbalance may reflect a significantly greater than expected increase in the risk of sudden death with the use of Mircera, a long-acting erythropoietin product, than with the use of shorter-acting reference agents.

The magnitude of the increase in risk appears to be greatest in hemoglobin maintenance therapy of renal anemia requiring hemodialysis, a setting in which patients with a relatively high treated "baseline" hemoglobin (near 12.0 g/dL) routinely experience dialysis-induced hematologic activation (complement system, platelets, other), sudden hemoconcentration, and potential electrolyte imbalance. The increase in the risk of sudden death may be magnified further in the presence of inflammation or infection. The increase in risk may be greater in hemoglobin maintenance than in anemia correction. These risk considerations may be applicable to serious adverse events other than sudden deaths.

Current erythropoietin product labels may not be adequate in assuring safety of erythropoietin therapy. In particular, the extent to which the hemoglobin may be safely increased above baseline likely differs with each patient (based on underlying disease and conditions). The current erythropoietin product labels specify 12.0 g/dL as the maximum hemoglobin. This recommendation is undesirable, since it implies that a hemoglobin level of 12.0 g/dL is based on clinical data and is applicable equally to all patients. Further, the value of 12.0 g/dL is often regarded in the clinical community as the desirable target rather than a maximum permissible hemoglobin level. The labeling for Mircera may be acceptable if:

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- The label states that the risk of serious adverse events including myocardial infarction, stroke, and sudden death have been shown to increased at target hemoglobin levels above 13.5 g/dL.

Sudden Death Adjudication

In an ongoing effort to evaluate the safety of Mircera, a Cardiovascular Mortality Adjudication Committee (CMAC) conducted a blinded evaluation of all deaths that occurred during Mircera clinical studies as of March 15, 2006 using pre-specified criteria for death categories.

- Death due to acute myocardial infarction (presence of two of the following): chest pain consistent with angina, any abnormal cardiac enzymes, and myocardial injury current or the development of Q waves in two contiguous ECG leads
- Death due to stroke (ischemic or hemorrhagic): an acute, focal neurologic event that occurred within 30 days of death
- Cardiovascular death: sudden or unexplained death lacking documentation of myocardial infarction or stroke
 - death from cardiac arrhythmia (observed to have had an arrhythmia)
 - Sudden death (etiology unspecified)
 - Death from congestive heart failure
- Non-cardiovascular death: deaths that were exclusive of the above described diagnoses
- Death due to discontinuation of dialysis (voluntary)

The CMAC independently reviewed and adjudicated all deaths (N=252) that occurred in Mircera clinical studies up to a data cutoff date of March 15, 2006. During their initial review, the committee requested and received additional information (SAE report forms and source documentation, if available) for 8 patients prior to completing the final adjudication. Consensus on the primary diagnosis was reached by simple majority during the first review cycle in all but 32 cases. Following discussion with all committee members at an adjudication teleconference meeting held on November 20, 2006, consensus on the diagnoses for these 32 cases was also reached as well. The results are shown in **Table 52**:

Table 52: Adjudicated Diagnoses of All Deaths

		RO0503821	Reference
All Studies			
All patients		1789	948
Patient died	NO	1624 (90.78%)	861 (90.82%)
	YES	165 (9.22%)	87 (9.18%)
Adjudicated Death Term	NON-CARDIOVASCULAR DEATH	56 (3.13%)	31 (3.27%)
	SUDDEN DEATH	35 (1.96%)	18 (1.90%)
	ARRHYTHMIA	18 (1.01%)	11 (1.16%)
	MYOCARDIAL INFARCTION	21 (1.17%)	6 (0.63%)
	DISCONTINUATION OF DIALYSIS	12 (0.67%)	9 (0.95%)
	CONGESTIVE HEART FAILURE	7 (0.39%)	5 (0.53%)
	HEMORRHAGIC STROKE	9 (0.50%)	3 (0.32%)
	ISCHEMIC STROKE	7 (0.39%)	3 (0.32%)
	STROKE*		1 (0.11%)

*diagnosis not further specified (lack of imaging data)

Review Comments

A comparison of crude mortality rates shown in **Table 46** and in **Table 52** shows an increase in mortality rates, as might be expected from extended reporting (from November 2005 through March 2006, 2.2% higher for Mircera and 3.1% higher for the reference agents). The small difference in crude mortality rate (0.9%) seen between the Mircera and the reference arms virtually disappeared (decreased further to 0.04%, as of March 2006). The initial imbalance in sudden deaths as reported by the clinical investigators (8 with Mircera, 0 with reference agents) also disappeared (1.96% with Mircera, 1.90% with reference agents). The term "sudden death" was selected more frequently by CMAC (53 times in total, 35 for Mircera and 18 for reference agents) than by the clinical investigators (9 times in total, all for Mircera). In interpreting the adjudicated "leveling" of the incidence of sudden deaths, it is important to note the differences between CMAC and the clinical investigators in the criteria for selecting the term "sudden death."

- CMAC: (all of the following)
 - sudden or unexplained death
 - no documentation of myocardial infarction or stroke
 - not observed to have had an arrhythmia
 - no indication of congestive heart failure
- Clinical investigators: (unspecified but probable criteria; both of the following)
 - unexpected death
 - unexplained death

Although the clinical investigators did not use pre-specified criteria in selecting the term "sudden death," the term was likely intended to indicate that the deaths were unexpected AND unexplained (occurred outside the hospital setting without medical evaluation near time of death). The adjudicated selection of the term "sudden death" was based on criteria that were independent of the "criteria" used by the clinical investigators, and the adjudicated and reported incidences of sudden death describe two independent clinical situations. The adjudication process, therefore, cannot explain or discredit the initial imbalance in sudden deaths as reported by the clinical

investigators; in the absence of a clear definition of "sudden death," the clinical investigators reported 8 "sudden deaths" with Mircera versus none with the reference agents, for whatever reason, in the controlled phase 3 studies. The imbalance in investigator-reported sudden deaths remains an important safety concern, and in the absence of a clear explanation, new clinical data may be needed to resolve this concern.

Safety Update as of September 1, 2006

As of September 1 (additional 10 months since BLA submission), the number and percentages of deaths increased in both groups: 39 deaths (4.1%) with the reference agents and 52 deaths (2.9%) with Mircera. The original and updated mortality indices are shown in **Table 53** (overall mortality), **Tables 54 and 55** (sudden deaths), and **Figure 15** (Kaplan-Meier plot).

Table 53: Updated Mortality Indices

EPO	Patients	Cut-Off	Deaths	CMR	PEY	AMR
Mircera	1789	11 - 2005	126	7.0	1532	8.2
		9 - 2006	182	10.2	2400	7.6
Reference	948	11 - 2005	58	6.1	778	7.5
		9 - 2006	103	10.9	1320	7.8

* Data shown apply to safety population (includes phase 2 data) for November 2005 cut-off, and extended population (safety population data extended to include extended follow up) for September 2006 cutoff; CMR = crude mortality rate (deaths per 100 patients); Cut-Off = date of data cut-off; EPO = erythropoietin product; PEY = patient exposure years; AMR = adjusted mortality rate (deaths per 100 PEY)

Table 54: Updated Indices for Sudden Deaths

EPO	Patients	Cut-Off	Deaths	CMR	PEY	AMR
Mircera	1789	11 - 2005	9**	0.50	1532	0.59
		9 - 2006	14	0.78	2400	0.58
Reference	948	11 - 2005	0	0	778	0
		9 - 2006	5	0.53	1320	0.38

* Data shown apply to safety population (includes phase 2 data) for November 2005 cut-off, and extended population (safety population data extended to include extended follow up) for September 2006 cutoff; ** Includes 1 death in phase 2 study; CMR = crude mortality rate (sudden deaths per

100 patients); Cut-Off = date of data cut-off; EPO = erythropoietin product; PEY = patient exposure years; AMR = adjusted mortality rate (sudden deaths per 100 PEY)

Table 55: Statistical Significance of Imbalance in Sudden Deaths

Cut-Off	EPO	Patients	Deaths	CMR	p-value
11 - 2005	Mircera	1789	9**	0.5	0.03
	Reference	948	0	0	
9 - 2006	Mircera	1789	14	0.8	0.4
	Reference	948	5	0.5	

* Data shown apply to safety population (includes phase 2 data) for November 2005 cut-off, and extended population (safety population data extended to include extended follow up) for September 2006 cutoff; ** Includes 1 death in phase 2 study; CMR = crude mortality rate (sudden deaths per 100 patients); *** Probability calculated using the chi-square test with 1 degree of freedom; Cut-Off = date of data cut-off; CMR = crude mortality rate (sudden deaths per 100 patients); EPO = erythropoietin product

Review Comments

Table 55 shows that the imbalance in sudden deaths in phase 3 studies (controlled) is statistically significant as of the November 2005 cut-off date (initial data lock), but not upon extended follow up as of the September 2006 cut-off date. The sponsor may have recognized sudden death as a potentially important safety concern at initial data analysis, and this recognition may have biased subsequent reporting in the open-label studies.

Figure 15: Updated Analysis of Time to Death

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SAE that occurred at a higher incidence in the reference group than in the Mircera group included: staphylococcal infection, hypercalcemia, back pain, and skin ulcer.

The percentage of patients with SAE that were considered by the investigator as related to study treatment was low and similar between groups (0.9% Mircera; 0.8% reference).

Overall Population

Overall, 37% of patients in the Mircera group and 40% in the reference group had one or more serious adverse events (SAE) during the study. The most frequently reported SAE in the Mircera group ($\geq 1.5\%$) were pneumonia and myocardial infarction as shown in **Table 56**. The incidence of these two most common SAE was similar between groups.

SAE that occurred in at least 0.5% of patients and more frequently in the Mircera group compared with the reference group included: GI hemorrhage (1.2 vs 0.2%). This event was also reported at a higher frequency in Mircera group vs the reference group when all AE (including serious and non-serious) were shown. SAE numerically higher in the Mircera group compared with the reference group included atrial fibrillation (1.0 vs 0.4%), acute myocardial infarction (0.8 vs 0.4%), angina unstable (0.5 vs 0.1%), and hypotension (0.8 vs 0.3%). When acute myocardial infarction and unstable angina were analyzed in context with other individual preferred terms referring to myocardial infarction, the incidence, regardless of severity, was comparable between groups (3% each group).

SAE that occurred in $> 0.5\%$ of patients with higher incidence in the reference group compared with the Mircera group included (reference vs Mircera): staphylococcal infection (0.5 vs 0.1%), hypercalcemia (0.5 vs 0.1%), back pain (0.5 vs 0.1%), and skin ulcer (0.7 vs 0.2%). SAE numerically higher in the reference group compared with the Mircera group included: gangrene (1.1 vs 0.5%), bacteremia (0.6 vs 0.2%), coronary artery disease (0.8 vs 0.4%), acute coronary syndrome (0.6 vs 0.2%), arteriovenous graft thrombosis (1.5 vs 0.8%), hip fracture (0.5 vs 0.2%), peripheral ischemia (0.8 vs 0.4%), hyperkalemia (1.2 vs 0.5%), chest pain (1.1 vs 0.5%), and catheter-related complication (0.5 vs 0.2%).

SAE of hypersensitivity or drug hypersensitivity were reported in 5 patients with Mircera and in 1 patient with the reference agents. Frequent ($\geq 0.5\%$) SAE are shown in **Table 56**.

Table 56: SAE with Incidence $> 0.5\%$ (Safety Population)

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Body System/ Adverse Event	RO0503821 N = 1789 No. (%)	Reference N = 948 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	660 (37)	383 (40)
Total Number of AEs	1280	772
INFECTIONS AND INFESTATIONS		
PNEUMONIA	43 (2.4)	29 (3.1)
SEPSIS	25 (1.4)	16 (1.7)
CELLULITIS	17 (1.0)	10 (1.1)
GANGRENE	9 (0.5)	10 (1.1)
URINARY TRACT INFECTION	9 (0.5)	6 (0.6)
GASTROENTERITIS	9 (0.5)	3 (0.3)
STAPHYLOCOCCAL BACTERAEMIA	7 (0.4)	5 (0.5)
ARTERIOVENOUS GRAFT SITE INFECTION	6 (0.3)	5 (0.5)
BACTERAEMIA	3 (0.2)	6 (0.6)
STAPHYLOCOCCAL INFECTION	1 (0.1)	5 (0.5)
CARDIAC DISORDERS		
MYOCARDIAL INFARCTION	30 (1.7)	18 (1.9)
CARDIAC FAILURE CONGESTIVE	25 (1.4)	16 (1.7)
CARDIAC ARREST	22 (1.2)	14 (1.5)
ATRIAL FIBRILLATION	17 (1.0)	4 (0.4)
ANGINA PECTORIS	13 (0.7)	7 (0.7)
ACUTE MYOCARDIAL INFARCTION	14 (0.8)	4 (0.4)
CARDIO-RESPIRATORY ARREST	11 (0.6)	5 (0.5)
CORONARY ARTERY DISEASE	8 (0.4)	8 (0.8)
ACUTE CORONARY SYNDROME	4 (0.2)	6 (0.6)
ANGINA UNSTABLE	9 (0.5)	1 (0.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
ARTERIOVENOUS FISTULA THROMBOSIS	23 (1.3)	16 (1.7)
ARTERIOVENOUS GRAFT THROMBOSIS	15 (0.8)	14 (1.5)
ARTERIOVENOUS FISTULA SITE HAEMORRHAGE	5 (0.3)	5 (0.5)
HIP FRACTURE	4 (0.2)	5 (0.5)
GASTROINTESTINAL DISORDERS		
GASTROINTESTINAL HAEMORRHAGE	21 (1.2)	2 (0.2)
NERVOUS SYSTEM DISORDERS		
SYNCOPE	9 (0.5)	3 (0.3)
CEREBROVASCULAR ACCIDENT	6 (0.3)	5 (0.5)
VASCULAR DISORDERS		
HYPOTENSION	14 (0.8)	3 (0.3)
HYPERTENSION	10 (0.6)	6 (0.6)
PERIPHERAL ISCHAEMIA	7 (0.4)	8 (0.8)
METABOLISM AND NUTRITION DISORDERS		
FLUID OVERLOAD	21 (1.2)	16 (1.7)
HYPERKALAEMIA	9 (0.5)	11 (1.2)
HYPOGLYCAEMIA	9 (0.5)	7 (0.7)
HYPERCALCAEMIA	2 (0.1)	5 (0.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
CHEST PAIN	9 (0.5)	10 (1.1)
CATHETER RELATED COMPLICATION	3 (0.2)	5 (0.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
PULMONARY OEDEMA	13 (0.7)	6 (0.6)
RENAL AND URINARY DISORDERS		
RENAL FAILURE CHRONIC	10 (0.6)	9 (0.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
BACK PAIN	1 (0.1)	5 (0.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
SKIN ULCER	3 (0.2)	7 (0.7)

RO0503821 = Mircera; Multiple occurrences of the same adverse event in one individual counted only once.

There was one case of serious hypersensitivity and one case of serious rash considered related in patients receiving Mircera in the overall safety population, and one case of serious related angioneurotic edema in a patient receiving a reference comparator.

Serious Hemorrhagic Events

Since GI hemorrhage was reported more frequently in the Mircera group than in the reference group, this event was analyzed in more detail. As a first step, all serious hemorrhagic events were pooled to determine if there was a difference between the Mircera and reference groups in the frequency of all hemorrhagic events for the overall safety population. Imbalances were seen in two of the hemoglobin maintenance studies (BA16739 and BA16740), which compared the efficacy and safety of Mircera administered either IV or SC in two treatment intervals (Q2W and Q4W) with epoetin (alfa or beta). The reported serious hemorrhagic events were grouped into four categories: upper GI hemorrhage, intracranial hemorrhage, vascular access hemorrhage, and other. This grouping (Table 57) shows that upper GI hemorrhage is more common in the Mircera group than in the reference group, while there is no excess of intracranial bleeding, or bleeding at the vascular access or other sites.

Table 57: Serious Hemorrhagic Events by Category

Category	RO0503821 N = 1789	Reference N = 948
Upper GI Hemorrhage	38 (2.1%)	9 (0.9%)
Intracranial Hemorrhage	13 (0.7%)	4 (0.4%)
Vascular Access Hemorrhage	13 (0.7%)	10 (1.0%)
Other	33 (1.8%)	14 (1.5%)

An analysis of concomitant medication affecting coagulation or mucosal integrity among patients with serious bleeding events showed that these agents were given slightly more frequently in the patients treated with Mircera than in patients treated with a reference drug (87 vs 66% for GI hemorrhage; 100 vs 75% for intracranial hemorrhage; 92 vs 100% for vascular access hemorrhage, 94 vs 93% for other, respectively). There was no relationship of serious hemorrhage to dose of Mircera.

As an exploratory approach, a logistic regression analysis was performed using the serious hemorrhagic events in the phase 3 studies only as the dependent variable and baseline risk factors as independent variables. Only phase 3 studies are included in this analysis because baseline risk factor data was specifically collected in these studies. All independent variables with a p value > 0.25 were excluded from the model using a backwards selection strategy. The results show that ischemic heart disease, GI hemorrhage, and vascular access hemorrhage at baseline are significant prognostic factors, while there is no effect of erythropoietin treatment.

7.1.3 Dropouts and Other Significant Adverse Events

Adverse Events Leading to Treatment Discontinuation

The incidence of AE leading to withdrawal was low and similar between the Mircera (2.5%) and reference groups (1.8%) in the overall safety population. No pattern in the types of AE leading to study discontinuation was observed in either treatment group.

In the overall pooled safety population, 2.5% of patients in the Mircera treatment group and 1.8% in the reference group had AE leading to withdrawal (**Table 58**). Adverse events that caused treatment discontinuation were varied and the incidence of each of these AE was low in both treatment groups. In the Mircera group, 10 of these events in 9 patients) were considered related to study treatment. In the reference group, 2 events in 2 patients) were considered related to study treatment.

The most frequent AE leading to study withdrawal in both treatment groups were cardiac disorders, renal and urinary disorders, and blood and lymphatic system disorders; the percentage of patients with AE in these body systems was similar between groups. Nervous system AE and neoplasms led to withdrawal more often in the Mircera group (6 vs 0 patients and 5 vs 1 patient, respectively). However, the number of withdrawals in each body system was very low in both groups (**Table 58**).

Since a subgroup analysis based on such small numbers would not give meaningful results, the summary of withdrawal includes the overall safety population only.

Table 58: Adverse Events Leading to Withdrawal (Overall Safety Population)

Body System/ Adverse Event	RO0503821		Reference	
	N = 1789		N = 948	
	No.	(%)	No.	(%)
ALL BODY SYSTEMS				
Total Pts with at Least one AE *	45	(3) *	17	(2) *
Total Number of AEs	46		18	
CARDIAC DISORDERS				
Total Pts With at Least one AE	5	(<1)	3	(<1)
CARDIAC ARREST	-		2	(<1)
CORONARY ARTERY DISEASE	2	(<1)	-	
AORTIC VALVE STENOSIS	1	(<1)	-	
CARDIAC FAILURE CONGESTIVE	1	(<1)	-	
MYOCARDIAL INFARCTION	-		1	(<1)
VENTRICULAR TACHYCARDIA	1	(<1)	-	
Total Number of AEs	5		3	

Adverse Events Leading to Dose Modification

The percentages of patients who had a dose modification for an AE in the overall safety population was lower in the Mircera group (103 patients, 6%) than in the reference group (106 patients, 11%). The most common AE leading to dose modification in both groups was anemia (18 patients, 1% in the Mircera group and 9 patients, < 1% in the reference group). Dose modifications included dose increases, dose decreases, and dose interruptions.

7.1.4 Other Search Strategies

Hemoglobin Rate of Change

Using a systematic approach of examining AE potentially associated with hemoglobin rate of rise, hyperphosphatemia was the only AE associated with hemoglobin increases of > 0.35 g/dL/week in both the Mircera and reference groups. The number of events in this quintile was small in both groups. Only two AE were potentially associated with hemoglobin decreases of $\geq$ 0.423 g/dL/week in both the Mircera and reference groups: GI hemorrhage and anemia. No consistent relationship was found between hemoglobin change and SAE or deaths.

Absolute Hemoglobin Level

Target Hemoglobin

Patients were enrolled in the hemoglobin maintenance studies at hemoglobin levels deemed appropriate by their treating physician and in the range of 10.5 to 13 g/dL. Hemoglobin values were to be maintained within the range of ± 1 g/dL of the baseline hemoglobin level, not to exceed 13.5 g/dL or fall below 10 g/dL, using the dose conversions and dose adjustment guideline provided in the protocols.

For patients enrolled in the anemia correction studies, a target hemoglobin > 11 g/dL was chosen in accordance with clinical practice and available treatment guidelines. Following anemia correction, patients were treated as in the hemoglobin maintenance studies using dose adjustment guidance provided in the protocols to maintain hemoglobin in the range of 11 to 13 g/dL. **Table 59** presents the relative frequencies of all hemoglobin values recorded in the phase 2 and phase 3 studies. Overall safety was assessed in the context of this practice for hemoglobin management.

Table 59: Number of Hemoglobin Values by Hemoglobin

Hemoglobin Class [g/dL]	RO0503821	Reference
<11	16668 (26.7%)	7474 (21.8%)
11-<12	17470 (28.0%)	11421 (33.3%)
12-<13	17232 (27.6%)	10541 (30.7%)
13-<14	8781 (14.1%)	4018 (11.7%)
≥ 14	2318 (3.7%)	865 (2.5%)

Based on all post-baseline values, duplicates are counted only once

Deaths in Relation to Absolute Hemoglobin Level

Overall there was a similar trend seen in both treatment groups for a higher percentage of deaths in the two lowest hemoglobin quintiles. By quintile, the percentages of deaths in each of the five increasing hemoglobin quintiles were (%): 29, 24, 13, 12, and 23 percent in the Mircera group and 41, 24, 16, 10, and 9 percent in the reference group (quintiles of < 10.6 , 10.6 to < 11.4 , 11.4 to < 12 , 12 to < 12.7 , and > 12.7 g/dL of hemoglobin, respectively). Using the same criteria used for AE, none of the deaths were associated with a particular hemoglobin level in both the Mircera or reference groups.

The results of the analysis of AE leading to death by quintiles is generally confirmed in the analysis by hemoglobin categories, but 23% of deaths occurred in the highest hemoglobin quintile in the Mircera group. A total of 15 of 126 AE leading to death (11.9%) occurred in association with hemoglobin values > 13 g/dL, which is lower than the prevalence of hemoglobin values > 13 g/dL (17.8%) in the population. In the > 14.0 g/dL category, there was a total of 6 of 126 AE leading to death (4.7%), which was slightly higher than the prevalence of hemoglobin values > 14.0 g/dL in the population (3.7%). However, these findings are based on very small numbers.